

Cytokine Inhibitors

APPLICATION DATA

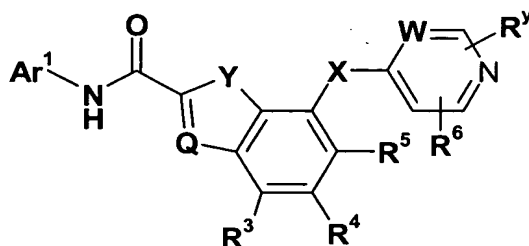
- 5 This application claims benefit to US provisional application no. 60/453,364 filed March 10, 2003.

BACKGROUND OF THE INVENTION

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1. TECHNICAL FIELD

This invention relates to compounds of formula (I)



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- The compounds of the invention inhibit production of cytokines involved in inflammatory processes and are thus useful for treating diseases and pathological conditions involving inflammation such as chronic inflammatory disease. This invention also relates to processes for preparing these compounds and to pharmaceutical compositions comprising these compounds.

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2. BACKGROUND INFORMATION

- Tumor necrosis factor (TNF) and interleukin-1 (IL-1) are important biological entities collectively referred to as proinflammatory cytokines which play a role in cytokine mediated diseases. These, along with several other related molecules, mediate the inflammatory response associated with the immunological recognition of infectious agents. The inflammatory response plays an important role in limiting and controlling pathogenic infections.

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Elevated levels of proinflammatory cytokines are also associated with a number of diseases of autoimmunity such as toxic shock syndrome, rheumatoid arthritis, osteoarthritis, diabetes and inflammatory bowel disease (Dinarello, C.A., *et al.*, 1984, *Rev. Infect. Disease* 6:51). In these diseases, chronic elevation of inflammation

5 exacerbates or causes much of the pathophysiology observed. For example, rheumatoid synovial tissue becomes invaded with inflammatory cells that result in destruction to cartilage and bone (Koch, A.E., *et al.*, 1995, *J. Invest. Med.* 43: 28-38). Studies suggest that inflammatory changes mediated by cytokines may be involved in endothelial cell pathogenesis including restenosis after percutaneous transluminal coronary angioplasty

10 (PTCA) (Tashiro, H., *et al.*, 2001 Mar, *Coron Artery Dis* 12(2):107-13). An important and accepted therapeutic approach for potential drug intervention in these diseases is the reduction of proinflammatory cytokines such as TNF (also referred to in its secreted cell-free form as TNF α) and IL-1 β . A number of anti-cytokine therapies are currently in clinical trials. Efficacy has been demonstrated with a monoclonal antibody directed

15 against TNF α in a number of autoimmune diseases (Heath, P., "CDP571: An Engineered Human IgG4 Anti-TNF α Antibody" IBC Meeting on Cytokine Antagonists, Philadelphia, PA, April 24-5, 1997). These include the treatment of rheumatoid arthritis, Crohn's disease and ulcerative colitis (Rankin, E.C.C., *et al.*, 1997, *British J. Rheum.* 35: 334-342 and Stack, W.A., *et al.*, 1997, *Lancet* 349: 521-524). The

20 monoclonal antibody is thought to function by binding to both soluble TNF α and to membrane bound TNF.

A soluble TNF α receptor has been engineered that interacts with TNF α . The approach is similar to that described above for the monoclonal antibodies directed against TNF α ;

25 both agents bind to soluble TNF α , thus reducing its concentration. One version of this construct, called Enbrel (Immunex, Seattle, WA) recently demonstrated efficacy in a Phase III clinical trial for the treatment of rheumatoid arthritis (Brower *et al.*, 1997, *Nature Biotechnology* 15: 1240). Another version of the TNF α receptor, Ro 45-2081 (Hoffman-LaRoche Inc., Nutley, NJ) has demonstrated efficacy in various animal

30 models of allergic lung inflammation and acute lung injury. Ro 45-2081 is a recombinant chimeric molecule constructed from the soluble 55 kDa human TNF receptor fused to the hinge region of the heavy chain IgG1 gene and expressed in eukaryotic cells (Renzetti, *et al.*, 1997, *Inflamm. Res.* 46: S143).

IL-1 has been implicated as an immunological effector molecule in a large number of disease processes. IL-1 receptor antagonist (IL-1ra) had been examined in human clinical trials. Efficacy has been demonstrated for the treatment of rheumatoid arthritis (Anril, Amgen). In a phase III human clinical trial IL-1ra reduced the mortality rate in patients with septic shock syndrome (Dinarelo, 1995, *Nutrition* 11, 492).

Osteoarthritis is a slow progressive disease characterized by destruction of the articular cartilage. IL-1 is detected in synovial fluid and in the cartilage matrix of osteoarthritic joints. Antagonists of IL-1 have been shown to diminish the degradation of cartilage matrix components in a variety of experimental models of arthritis (Chevalier, 1997, *Biomed Pharmacother.* 51, 58). Nitric oxide (NO) is a mediator of cardiovascular homeostasis, neurotransmission and immune function; recently it has been shown to have important effects in the modulation of bone remodeling. Cytokines such as IL-1 and TNF are potent stimulators of NO production. NO is an important regulatory molecule in bone with effects on cells of the osteoblast and osteoclast lineage (Evans, *et al.*, 1996, *J Bone Miner Res.* 11, 300). The promotion of beta-cell destruction leading to insulin dependent diabetes mellitus shows dependence on IL-1. Some of this damage may be mediated through other effectors such as prostaglandins and thromboxanes. IL-1 can effect this process by controlling the level of both cyclooxygenase II and inducible nitric oxide synthetase expression (McDaniel *et al.*, 1996, *Proc Soc Exp Biol Med.* 211, 24).

Inhibitors of cytokine production are expected to block inducible cyclooxygenase (COX-2) expression. COX-2 expression has been shown to be increased by cytokines and it is believed to be the isoform of cyclooxygenase responsible for inflammation (M.K. O'Banion *et al.*, *Proc. Natl. Acad. Sci. U.S.A.*, 1992, 89, 4888.) Accordingly, inhibitors of cytokines such as IL-1 would be expected to exhibit efficacy against those disorders currently treated with COX inhibitors such as the familiar NSAIDs. These disorders include acute and chronic pain as well as symptoms of inflammation and cardiovascular disease.

Elevation of several cytokines have been demonstrated during active inflammatory bowel disease (IBD). A mucosal imbalance of intestinal IL-1 and IL-1ra is present in

patients with IBD. Insufficient production of endogenous IL-1ra may contribute to the pathogenesis of IBD (Cominelli, *et al.*, 1996, *Aliment Pharmacol Ther.* 10, 49).

Alzheimer disease is characterized by the presence of beta-amyloid protein deposits, neurofibrillary tangles and cholinergic dysfunction throughout the hippocampal region.

- 5 The structural and metabolic damage found in Alzheimer disease is possibly due to a sustained elevation of IL-1 (Holden, *et al.*, 1995, *Med Hypotheses*, 45, 559). A role for IL-1 in the pathogenesis of human immunodeficiency virus (HIV) has been identified. IL-1ra showed a clear relationship to acute inflammatory events as well as to the different disease stages in the pathophysiology of HIV infection (Kreuzer, *et al.*, 1997, Clin Exp Immunol. 109, 54). IL-1 and TNF are both involved in periodontal disease. 10 The destructive process associated with periodontal disease may be due to a dysregulation of both IL-1 and TNF (Howells, 1995, *Oral Dis.* 1, 266).

- Proinflammatory cytokines such as TNF α and IL-1 β are also important mediators of 15 septic shock and associated cardiopulmonary dysfunction, acute respiratory distress syndrome (ARDS) and multiple organ failure. In a study of patients presenting at a hospital with sepsis, a correlation was found between TNF α and IL-6 levels and septic complications (Terregino *et al.*, 2000, *Ann. Emerg. Med.*, 35, 26). TNF α has also been implicated in cachexia and muscle degradation, associated with HIV infection 20 (Lahdiverta *et al.*, 1988, *Amer. J. Med.*, 85, 289). Obesity is associated with an increase incidence of infection, diabetes and cardiovascular disease. Abnormalities in TNF α expression have been noted for each of the above conditions (Loffreda, *et al.*, 1998, *FASEB J.* 12, 57). It has been proposed that elevated levels of TNF α are involved in other eating related disorders such as anorexia and bulimia nervosa. Pathophysiological 25 parallels are drawn between anorexia nervosa and cancer cachexia (Holden, *et al.*, 1996, *Med Hypotheses* 47, 423). An inhibitor of TNF α production, HU-211, was shown to improve the outcome of closed brain injury in an experimental model (Shohami, *et al.*, 1997, *J Neuroimmunol.* 72, 169). Atherosclerosis is known to have an inflammatory component and cytokines such as IL-1 and TNF have been suggested to promote the 30 disease. In an animal model an IL-1 receptor antagonist was shown to inhibit fatty streak formation (Elhage *et al.*, 1998, *Circulation*, 97, 242).

TNF α levels are elevated in airways of patients with chronic obstructive pulmonary disease and it may contribute to the pathogenesis of this disease (M.A. Higham *et al.*, 2000, *Eur. Respiratory J.*, 15, 281). Circulating TNF α may also contribute to weight loss associated with this disease (N. Takabatake *et al.*, 2000, *Amer. J. Resp. & Crit. Care Med.*, 161 (4 Pt 1), 1179). Elevated TNF α levels have also been found to be associated with congestive heart failure and the level has been correlated with severity of the disease (A.M. Feldman *et al.*, 2000, *J. Amer. College of Cardiology*, 35, 537). In addition, TNF α has been implicated in reperfusion injury in lung (Borjesson *et al.*, 2000, *Amer. J. Physiol.*, 278, L3-12), kidney (Lemay *et al.*, 2000, *Transplantation*, 69, 959), and the nervous system (Mitsui *et al.*, 1999, *Brain Res.*, 844, 192).

TNF α is also a potent osteoclastogenic agent and is involved in bone resorption and diseases involving bone resorption (Abu-Amer *et al.*, 2000, *J. Biol. Chem.*, 275, 27307). It has also been found highly expressed in chondrocytes of patients with traumatic arthritis (Melchiorri *et al.*, 2000, *Arthritis and Rheumatism*, 41, 2165). TNF α has also been shown to play a key role in the development of glomerulonephritis (Le Hir *et al.*, 1998, *Laboratory Investigation*, 78, 1625).

The abnormal expression of inducible nitric oxide synthetase (iNOS) has been associated with hypertension in the spontaneously hypertensive rat (Chou *et al.*, 1998, *Hypertension*, 31, 643). IL-1 has a role in the expression of iNOS and therefore may also have a role in the pathogenesis of hypertension (Singh *et al.*, 1996, *Amer. J. Hypertension*, 9, 867).

IL-1 has also been shown to induce uveitis in rats which could be inhibited with IL-1 blockers. (Xuan *et al.*, 1998, *J. Ocular Pharmacol. and Ther.*, 14, 31). Cytokines including IL-1, TNF and GM-CSF have been shown to stimulate proliferation of acute myelogenous leukemia blasts (Bruserud, 1996, *Leukemia Res.* 20, 65). IL-1 was shown to be essential for the development of both irritant and allergic contact dermatitis. Epicutaneous sensitization can be prevented by the administration of an anti- IL-1 monoclonal antibody before epicutaneous application of an allergen (Muller, *et al.*, 1996, *Am J Contact Dermat.* 7, 177). Data obtained from IL-1 knock out mice indicates the critical involvement in fever for this cytokine (Kluger *et al.*, 1998, *Clin Exp*

Pharmacol Physiol. 25, 141). A variety of cytokines including TNF, IL-1, IL-6 and IL-8 initiate the acute-phase reaction which is stereotyped in fever, malaise, myalgia, headaches, cellular hypermetabolism and multiple endocrine and enzyme responses (Beisel, 1995, *Am J Clin Nutr.* 62, 813). The production of these inflammatory
 5 cytokines rapidly follows trauma or pathogenic organism invasion.

Other proinflammatory cytokines have been correlated with a variety of disease states. IL-8 correlates with influx of neutrophils into sites of inflammation or injury. Blocking antibodies against IL-8 have demonstrated a role for IL-8 in the neutrophil associated
 10 tissue injury in acute inflammation (Harada *et al.*, 1996, *Molecular Medicine Today* 2, 482). Therefore, an inhibitor of IL-8 production may be useful in the treatment of diseases mediated predominantly by neutrophils such as stroke and myocardial infarction, alone or following thrombolytic therapy, thermal injury, adult respiratory distress syndrome (ARDS), multiple organ injury secondary to trauma, acute
 15 glomerulonephritis, dermatoses with acute inflammatory components, acute purulent meningitis or other central nervous system disorders, hemodialysis, leukopheresis, granulocyte transfusion associated syndromes, and necrotizing enterocolitis.

Rhinovirus triggers the production of various proinflammatory cytokines,
 20 predominantly IL-8, which results in symptomatic illnesses such as acute rhinitis (Winther *et al.*, 1998, *Am J Rhinol.* 12, 17).

Other diseases that are effected by IL-8 include myocardial ischemia and reperfusion, inflammatory bowel disease and many others.

25 The proinflammatory cytokine IL-6 has been implicated with the acute phase response. IL-6 is a growth factor in a number in oncological diseases including multiple myeloma and related plasma cell dyscrasias (Treon, *et al.*, 1998, *Current Opinion in Hematology* 5: 42). It has also been shown to be an important mediator of inflammation within the
 30 central nervous system. Elevated levels of IL-6 are found in several neurological disorders including AIDS dementia complex, Alzheimer's disease, multiple sclerosis, systemic lupus erythematosus, CNS trauma and viral and bacterial meningitis (Gruol, *et al.*, 1997, *Molecular Neurobiology* 15: 307). IL-6 also plays a significant role in

osteoporosis. In murine models it has been shown to effect bone resorption and to induce osteoclast activity (Ershler *et al.*, 1997, *Development and Comparative Immunol.* 21: 487). Marked cytokine differences, such as IL-6 levels, exist in vivo between osteoclasts of normal bone and bone from patients with Paget's disease (Mills, *et al.*, 5 1997, *Calcif Tissue Int.* 61, 16). A number of cytokines have been shown to be involved in cancer cachexia. The severity of key parameters of cachexia can be reduced by treatment with anti IL-6 antibodies or with IL-6 receptor antagonists (Strassmann, *et al.*, 1995, *Cytokines Mol Ther.* 1, 107). Several infectious diseases, such as influenza, indicate IL-6 and IFN alpha as key factors in both symptom formation and in host 10 defense (Hayden, *et al.*, 1998, *J Clin Invest.* 101, 643). Overexpression of IL-6 has been implicated in the pathology of a number of diseases including multiple myeloma, rheumatoid arthritis, Castleman's disease, psoriasis and post-menopausal osteoporosis (Simpson, *et al.*, 1997, *Protein Sci.* 6, 929). Compounds that interfered with the production of cytokines including IL-6, and TNF were effective in blocking a passive 15 cutaneous anaphylaxis in mice (Scholz *et al.*, 1998, *J. Med. Chem.*, 41, 1050).

GM-CSF is another proinflammatory cytokine with relevance to a number of therapeutic diseases. It influences not only proliferation and differentiation of stem cells but also regulates several other cells involved in acute and chronic inflammation. 20 Treatment with GM-CSF has been attempted in a number of disease states including burn-wound healing, skin-graft resolution as well as cytostatic and radiotherapy induced mucositis (Masucci, 1996, *Medical Oncology* 13: 149). GM-CSF also appears to play a role in the replication of human immunodeficiency virus (HIV) in cells of macrophage lineage with relevance to AIDS therapy (Crowe *et al.*, 1997, *Journal of Leukocyte 25 Biology* 62, 41). Bronchial asthma is characterised by an inflammatory process in lungs. Involved cytokines include GM-CSF amongst others (Lee, 1998, *J R Coll Physicians Lond* 32, 56).

Interferon γ (IFN γ) has been implicated in a number of diseases. It has been associated 30 with increased collagen deposition that is a central histopathological feature of graft-versus-host disease (Parkman, 1998, *Curr Opin Hematol.* 5, 22). Following kidney transplantation, a patient was diagnosed with acute myelogenous leukemia. Retrospective analysis of peripheral blood cytokines revealed elevated levels of GM-

CSF and IFN γ . These elevated levels coincided with a rise in peripheral blood white cell count (Burke, *et al.*, 1995, *Leuk Lymphoma*. 19, 173). The development of insulin-dependent diabetes (Type 1) can be correlated with the accumulation in pancreatic islet cells of T-cells producing IFN γ (Ablumunits, *et al.*, 1998, *J Autoimmun*. 11, 73). IFN γ along with TNF, IL-2 and IL-6 lead to the activation of most peripheral T-cells prior to the development of lesions in the central nervous system for diseases such as multiple sclerosis (MS) and AIDS dementia complex (Martino *et al.*, 1998, *Ann Neurol*. 43, 340). Atherosclerotic lesions result in arterial disease that can lead to cardiac and cerebral infarction. Many activated immune cells are present in these lesions, mainly T-cells and macrophages. These cells produce large amounts of proinflammatory cytokines such as TNF, IL-1 and IFN γ . These cytokines are thought to be involved in promoting apoptosis or programmed cell death of the surrounding vascular smooth muscle cells resulting in the atherosclerotic lesions (Geng, 1997, *Heart Vessels Suppl* 12, 76). Allergic subjects produce mRNA specific for IFN γ following challenge with *Vesputa* venom (Bonay, *et al.*, 1997, *Clin Exp Immunol*. 109, 342). The expression of a number of cytokines, including IFN γ has been shown to increase following a delayed type hypersensitivity reaction thus indicating a role for IFN γ in atopic dermatitis (Szepietowski, *et al.*, 1997, *Br J Dermatol*. 137, 195). Histopathologic and immunohistologic studies were performed in cases of fatal cerebral malaria. Evidence for elevated IFN γ amongst other cytokines was observed indicating a role in this disease (Udomsangpetch *et al.*, 1997, *Am J Trop Med Hyg*. 57, 501). The importance of free radical species in the pathogenesis of various infectious diseases has been established. The nitric oxide synthesis pathway is activated in response to infection with certain viruses via the induction of proinflammatory cytokines such as IFN γ (Akaike, *et al.*, 1998, *Proc Soc Exp Biol Med*. 217, 64). Patients, chronically infected with hepatitis B virus (HBV) can develop cirrhosis and hepatocellular carcinoma. Viral gene expression and replication in HBV transgenic mice can be suppressed by a post-transcriptional mechanism mediated by IFN γ , TNF and IL-2 (Chisari, *et al.*, 1995, *Springer Semin Immunopathol*. 17, 261). IFN γ can selectively inhibit cytokine induced bone resorption. It appears to do this via the intermediacy of nitric oxide (NO) which is an important regulatory molecule in bone remodeling. NO may be involved as a mediator of bone disease for such diseases as: rheumatoid arthritis, tumor associated osteolysis and postmenopausal osteoporosis (Evans, *et al.*, 1996, *J Bone Miner Res*. 11,

- 300). Studies with gene deficient mice have demonstrated that the IL-12 dependent production of IFN γ is critical in the control of early parasitic growth. Although this process is independent of nitric oxide the control of chronic infection does appear to be NO dependent (Alexander *et al.*, 1997, *Philos Trans R Soc Lond B Biol Sci* 352, 1355).
- 5 NO is an important vasodilator and convincing evidence exists for its role in cardiovascular shock (Kilbourn, *et al.*, 1997, *Dis Mon.* 43, 277). IFN γ is required for progression of chronic intestinal inflammation in such diseases as Crohn's disease and inflammatory bowel disease (IBD) presumably through the intermediacy of CD4+ lymphocytes probably of the TH1 phenotype (Sartor 1996, *Aliment Pharmacol Ther.* 10
- 10 *Suppl* 2, 43). An elevated level of serum IgE is associated with various atopic diseases such as bronchial asthma and atopic dermatitis. The level of IFN γ was negatively correlated with serum IgE suggesting a role for IFN γ in atopic patients (Teramoto *et al.*, 1998, *Clin Exp Allergy* 28, 74).
- 15 WO 01/01986 discloses particular compounds alleged to having the ability to inhibit TNF-alpha. Certain compounds disclosed in WO 01/01986 are indicated to be effective in treating the following diseases: dementia associated with HIV infection, glaucoma, optic-neuropathy, optic neuritis, retinal ischemia, laser induced optic damage, surgery or trauma-induced proliferative vitreoretinopathy, cerebral ischemia, hypoxia-ischemia,
- 20 hypoglycemia, domoic acid poisoning, anoxia, carbon monoxide or manganese or cyanide poisoning, Huntington's disease, Alzheimer's disease, Parkinson's disease, meningitis, multiple sclerosis and other demyelinating diseases, amyotrophic lateral sclerosis, head and spinal cord trauma, seizures, convulsions, olivopontocerebellar atrophy, neuropathic pain syndromes, diabetic neuropathy, HIV-related neuropathy,
- 25 MERRF and MELAS syndromes, Leber's disease, Wernicke's encephalopathy, Rett syndrome, homocysteinuria, hyperprolinemia, hyperhomocysteinemia, nonketotic hyperglycinemia, hydroxybutyric aminoaciduria, sulfite oxidase deficiency, combined systems disease, lead encephalopathy, Tourett's syndrome, hepatic encephalopathy, drug addiction, drug tolerance, drug dependency, depression, anxiety and schizophrenia.
- 30 WO 02/32862 discloses that inhibitors of pro-inflammatory cytokines including TNF α are allegedly useful for treating acute and chronic inflammation in the lung caused by inhalation of smoke such as cigarette smoke. TNF α antagonists are apparently also useful for the treatment of endometriosis, see EP 1022027 A1. Infliximab, in clinical

trials for RA, has also been indicated to be useful for treating various inflammatory diseases including Behcet's disease, uveitis and ankylosing spondylitis. Pancreatitis may also be regulated by inflammatory mediator production, see J Surg Res 2000 May 15 90(2)95-101; Shock 1998 Sep. 10(3):160-75. p38MAP kinase pathway plays an role
5 in B.burgdorferi-elicited inflammation and may be useful in treating inflammation induced by the Lyme disease agent. Anguita, J. et. al., *The Journal of Immunology*, 2002,168:6352-6357.

Compounds which modulate release of one or more of the aforementioned
10 inflammatory cytokines can be useful in treating diseases associated with release of these cytokines. For example, WO 98/52558 discloses heteroaryl urea compounds which are indicated to be useful in treating cytokine mediated diseases. WO 99/23091 discloses another class of urea compounds which are useful as anti-inflammatory agents. WO 99/32463 relates to aryl ureas and their use in treating cytokine diseases
15 and proteolytic enzyme mediated disease. WO 00/41698 discloses aryl ureas said to be useful in treating p38 MAP kinase diseases.

Compounds active against p38 MAP kinase can also be useful for treating various types of cancers as described in WO 03/068223.

20 U.S. Pat. No. 5,162,360 discloses N-substituted aryl-N'-heterocyclic substituted urea compounds which are described as being useful for treating hypercholesterolemia and atherosclerosis. Di-substituted aryl and heteroaryl compounds are also disclosed in US Pat. Nos. 6,080,763; 6,319,921; 6,297,381 and 6,358,945. The compounds in the patents
25 are alleged to possess anti-cytokine activity and are therefore useful in treating diseases associated with inflammation.

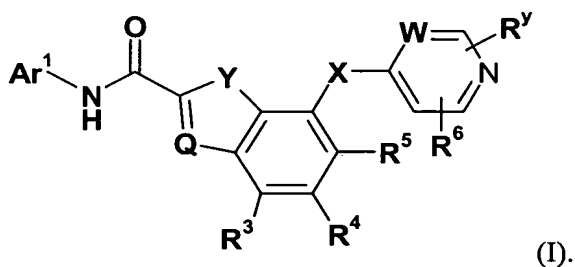
The work cited above supports the principle that inhibition of cytokine production will be beneficial in the treatment of cytokine mediated diseases. Therefore a need exists for
30 small molecule inhibitors for treating these diseases with optimized efficacy, pharmacokinetic and safety profiles.

BRIEF SUMMARY OF THE INVENTION

The work cited above supports the principle that inhibition of cytokine production with small molecule compounds will be beneficial in the treatment of various disease states.

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It is therefore an object of the invention to provide compounds of formula (I)



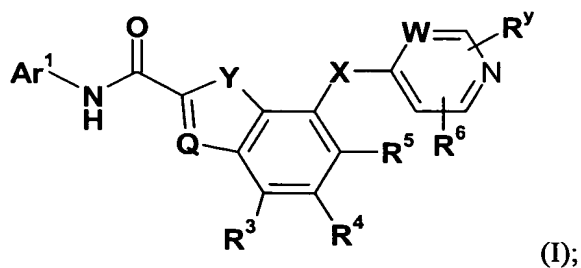
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It is a further object of the invention to provide methods for treating cytokine mediated diseases and pathological conditions involving inflammation such as chronic inflammatory disease, using the novel compounds of the invention.

15 It is yet a further object of the invention to provide pharmaceutical compositions and processes of preparation of the above-mentioned novel compounds.

20 DETAILED DESCRIPTION OF THE INVENTION

In the broadest generic embodiment, there is provided compounds of the formula (I)



wherein:

Ar¹ is an aromatic carbocycle substituted with one **R¹**, and wherein **Ar¹** is independently substituted with two **R²** groups and wherein one **R¹** and one **R²** on adjacent ring atoms optionally form a 5- or 6-membered carbocyclic or heterocyclic ring;

R¹ is halogen, NO₂, NH₂, **J-N(R^a)-(CH₂)_m-**, **N(J)₂-(CH₂)_m-**, **NH₂C(O)-**, **J-N(R^a)-C(O)-**, **J-S(O)_m-N(R^a)-**, **J-N(R^a)-S(O)_m-** or heterocycle-(CH₂)_m- wherein the heterocyclic group is optionally substituted by C₁₋₅ alkyl;

Q is a N or CR^P;

Y is >CR^PR^v, -CR^P=C(R^v)-, -O-, -N(R^x)- or >S(O)_m;

wherein **R^a**, **R^P**, **R^v**, **R^x** and **R^y** are each independently hydrogen or C₁₋₅ alkyl;

X is -CH₂-, -N(R^a)-, -O- or -S-;

W is N or CH;

each **m** is independently 0, 1 or 2;

J is chosen from C1-10 alkyl and carbocycle each optionally substituted by **R^b**;

R² is chosen from C1-6 alkyl, C3-7 cycloalkyl optionally substituted by C1-5 alkyl, C1-4 acyl, aroyl, C1-4 alkoxy, each being optionally partially or fully halogenated, halogen, C1-6 alkoxycarbonyl, carbocyclesulfonyl and -SO₂-CF₃;

each **R³**, **R⁴** and **R⁵** are independently chosen from hydrogen, C1-6 alkyl and halogen;

R⁶ is optionally attached at a position *ortho* or *meta* to the N atom of the indicated ring, and is chosen from

a bond, -O-, -O-(CH₂)₁₋₅-, >C(O), -NH-, -C(O)-NH-, -S-, C₁₋₅ alkyl branched or unbranched, C₂₋₅ alkenyl, C₁₋₃ acyl, C₁₋₃ alkyl(OH), heterocycle selected from morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl and tetrahydrofuranyl, heteroaryl selected from pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, isoxazolyl, thiazolyl, oxazolyl and isothiazolyl or aryl each alkyl, alkenyl, acyl, heterocycle, heteroaryl and aryl are optionally substituted by one to three hydroxy, oxo, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₁₋₅ alkoxycarbonyl, -NR₇R₈ or NR₇R₈-C(O)-;

wherein each R₆ is further optionally covalently attached to groups chosen from:
 hydrogen, -NR₇R₈, C₁₋₃ alkyl, C₃₋₆ cycloalkylC₀₋₂alkyl, hydroxy, C₁₋₃ alkoxy, phenoxy, benzyloxy, arylC₀₋₄ alkyl, heteroaryl C₀₋₄ alkyl and heterocycle C₀₋₄alkyl, each above-listed heterocycle, heteroaryl and aryl group is optionally substituted by one to three hydroxy, oxo, C₁₋₄ alkyl, C₁₋₃ alkoxy, C₁₋₅ alkoxycarbonyl, NR₇R₈-C(O)- or C₁₋₄ acyl;

each R₇ and R₈ are independently hydrogen, phenylC₀₋₃alkyl optionally substituted by halogen, C₁₋₃ alkyl or diC₁₋₅ alkyl amino, or R₇ and R₈ are C₁₋₂ acyl, benzoyl or C₁₋₅ branched or unbranched alkyl optionally substituted by C₁₋₄ alkoxy, hydroxy or mono or diC₁₋₃ alkyl amino;

and
 R^b is chosen from hydrogen, C₁₋₅ alkyl, hydroxyC₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, carbocycle, heterocycle, heteroaryl, C₁₋₅ alkoxy, C₁₋₅ alkylthio, amino, C₁₋₅ alkylamino, C₁₋₅ dialkylamino, C₁₋₅ acyl, C₁₋₅ alkoxycarbonyl, C₁₋₅ acyloxy, C₁₋₅ acylamino, each of the aforementioned are optionally partially or fully halogenated, or R^b is chosen from C₁₋₅ alkylsulphonylamino, hydroxy, oxo, halogen, nitro and nitrile;

or the pharmaceutically acceptable salts, acids, esters or isomers thereof.

In another embodiment, there are provided compounds of the formula (I) as described above and wherein

Y is -O-, -S-, -NH-, -N(CH₂CH₃)- or -N(CH₃)-;

X is -N(R^a)-, or -O- ;

5 **Q** is CH;

J is chosen from C1-10 alkyl, aryl or C3-7 cycloalkyl each optionally substituted by R^b;

10 **R**₂ is independently chosen from C1-6 alkyl, C3-6 cycloalkyl optionally substituted by C1-3 alkyl, acetyl, aroyl, C1-5 alkoxy, each being optionally partially or fully halogenated, halogen, methoxycarbonyl, phenylsulfonyl and -SO₂-CF₃;

each R³, R⁴ and R⁵ are hydrogen;

15

R^b is chosen from hydrogen, C1-5 alkyl, C2-5 alkenyl, C2-5 alkynyl, C3-8 cycloalkyl, C0-2 alkyl, aryl, C1-5 alkoxy, C1-5 alkylthio, amino, C1-5 alkylamino, C1-5 dialkylamino, C1-5 acyl, C1-5 alkoxycarbonyl, C1-5 acyloxy, C1-5 acylamino, C1-5 sulphonylamino, hydroxy, halogen, trifluoromethyl, nitro, nitrile
20 or R^b is chosen from; heterocycle chosen from pyrrolidinyl, pyrrolinyl, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, dioxalanyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxanyl, piperidinonyl, tetrahydropyrimidinyl,
25 pentamethylene sulfide, pentamethylene sulfoxide, pentamethylene sulfone, tetramethylene sulfide, tetramethylene sulfoxide and tetramethylene sulfone and heteroaryl chosen from aziridinyl, thienyl, furanyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, tetrazolyl, pyrazolyl, pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyranyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl,
30 benzothiazolyl, benzothienyl, quinolinyl, quinazolinyl, naphthyridinyl, indazolyl, triazolyl, pyrazolo[3,4-*b*]pyrimidinyl, purinyl, pyrrolo[2,3-*b*]pyridinyl, pyrazolo[3,4-*b*]pyridinyl, tubercidinyl, oxazo[4,5-*b*]pyridinyl and imidazo[4,5-*b*]pyridinyl.

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In yet another embodiment, there are provided compounds of the formula (I) as described immediately above and wherein

- 5 **Ar**¹ is chosen from phenyl, naphthyl, tetrahydronaphthyl, indanyl and indenyl, each **Ar**¹ is optionally substituted with one **R**¹, and independently substituted with two **R**² groups;

Y is -O-, -S- or -N(CH₃)-;

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R⁶ is present, and is chosen from
 a bond, -O-, -O-(CH₂)₁₋₅-, -NH-, -C(O)-NH-, C₁₋₅ alkyl branched or unbranched, C₂₋₅ alkenyl, C₁₋₃ alkyl(OH), heterocycle selected from morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl and tetrahydrofuranyl, or aryl chosen from phenyl and naphthyl, each
 15 alkyl, alkenyl, heterocycle and aryl are optionally substituted by one to three hydroxy, C₁₋₃ alkyl, C₁₋₃ alkoxy, mono or diC₁₋₃ alkyl amino, amino or C₁₋₅ alkoxycarbonyl;

wherein each **R**₆ is further optionally covalently attached to groups chosen from:

- hydrogen, -NR₇R₈, C₁₋₃ alkyl, C₃₋₆ cycloalkylC₀₋₂alkyl, hydroxy, C₁₋₃ alkoxy,
 20 phenoxy, benzyloxy, phenylC₀₋₄ alkyl, piperazinylC₀₋₄ alkyl, piperidinyl C₀₋₄alkyl, pyrrolidinylC₀₋₄ alkyl, morpholinylC₀₋₄ alkyl, tetrahydrofuranylC₀₋₄ alkyl, triazolyl C₀₋₄alkyl, imidazolyl C₀₋₄alkyl and pyridinyl C₀₋₄alkyl, each abovelisted heterocycle, heteroaryl and phenyl group is optionally substituted by one to three hydroxy, oxo, C₁₋₄ alkyl, C₁₋₃ alkoxy, C₁₋₅ alkoxycarbonyl, -NR₇R₈, NR₇R₈-C(O)- or C₁₋₄ acyl;

25

each **R**₇ and **R**₈ are independently hydrogen, phenylC₀₋₃alkyl optionally substituted by halogen, C₁₋₃ alkyl or diC₁₋₅ alkyl amino, or **R**₇ and **R**₈ are C₁₋₂ acyl, benzoyl or C₁₋₅ branched or unbranched alkyl optionally substituted by C₁₋₄ alkoxy, hydroxy or mono or diC₁₋₃ alkyl amino.

30

In yet another embodiment, there are provided compounds of the formula (I) as described immediately above and wherein

X is -O- ;

Y is -N(CH₃)-;

5 **J** is C1-10 alkyl optionally substituted by **R^b**;

R₂ is independently chosen from C1-6 alkyl, C3-6 cycloalkyl optionally substituted by C1-3 alkyl and C1-5 alkoxy, each being optionally be partially or fully halogenated;

10 **R⁶** is chosen from
 a bond, -O-, -O-(CH₂)₁₋₅-, -NH-, -C(O)-NH-, C₁₋₅ alkyl branched or unbranched, C₂₋₅ alkenyl, C₁₋₃ alkyl(OH), heterocycle selected from morpholinyl, piperazinyl, piperidinyl and pyrrolidinyl or phenyl, each alkyl, alkenyl, heterocycle and phenyl are optionally substituted by one to three hydroxy, C₁₋₃ alkyl, C₁₋₃ alkoxy, mono or diC₁₋₃ alkyl amino,
 15 amino or C₁₋₅ alkoxycarbonyl;

wherein each **R₆** is further optionally covalently attached to groups chosen from:

hydrogen, -NR₇R₈, C₁₋₃ alkyl, C₃₋₆ cycloalkylC₀₋₂alkyl, benzyloxy, phenylC₀₋₄ alkyl, piperazinylC₀₋₄ alkyl, piperidinyl C₀₋₄alkyl, pyrrolidinylC₀₋₄ alkyl, morpholinylC₀₋₄
 20 alkyl, triazolyl C₀₋₄alkyl, imidazolyl C₀₋₄alkyl and pyridinyl C₀₋₄alkyl, each above-listed heterocycle, heteroaryl and phenyl group is optionally substituted by one to three hydroxy, oxo, C₁₋₄ alkyl, C₁₋₃ alkoxy, C₁₋₅ alkoxycarbonyl, amino, NR₇R₈-C(O)- or C₁₋₄ acyl;

25 each **R₇** and **R₈** are independently hydrogen, phenylC₀₋₂alkyl optionally substituted by halogen, C₁₋₃ alkyl or diC₁₋₅ alkyl amino, or **R₇** and **R₈** are C₁₋₅ branched or unbranched alkyl optionally substituted by C₁₋₄ alkoxy, hydroxy or mono or diC₁₋₃ alkyl amino;

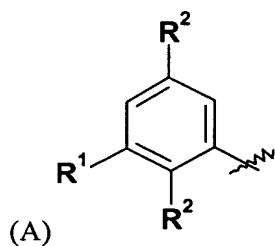
R^b is chosen from hydrogen, C1-5 alkyl, C3-7 cycloalkylC₀₋₂ alkyl, aryl, C1-5 alkoxy,
 30 amino, C1-5 alkylamino, C1-3 dialkylamino, C1-3 acyl, C1-5 alkoxycarbonyl, C1-3 acyloxy, C1-3 acylamino, C1-3 sulphonylamino, hydroxy, halogen, trifluoromethyl, nitro, nitrile;

or R^b is chosen from pyrrolidinyl, pyrrolinyl, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, piperidinyl, piperazinyl, piperidinonyl, tetrahydropyrimidinonyl, aziridinyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, tetrazolyl, pyrazolyl, pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl.

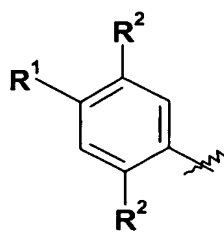
In yet still another embodiment, there are provided compounds of the formula (I) as described immediately above and wherein

10

Ar^1 is formula (A) or (B)



or



wherein:

15

when Ar^1 is formula (A) then:

R^1 is NH_2 , $J-N(R^a)-(CH_2)_m-$, $NH_2C(O)-$, $J-N(R^a)-C(O)-$, $J-S(O)_2-N(R^a)-$, $J-N(R^a)-S(O)_2-$ or heterocycle- $(CH_2)_{1-2}-$ wherein the heterocycle is chosen from pyrrolidinyl, morpholinyl and piperazinyl each optionally substituted by C1-4 alkyl, and J is C₁₋₅ alkyl optionally substituted by R^b ;

20

or

when Ar^1 is formula (B) then:

R^1 is hydrogen or halogen;

25

R_2 is independently chosen from C1-5 alkyl, C3-6 cycloalkyl optionally substituted by C1-3 alkyl and C1-5 alkoxy, each being optionally partially or fully halogenated;

R^6 is chosen from

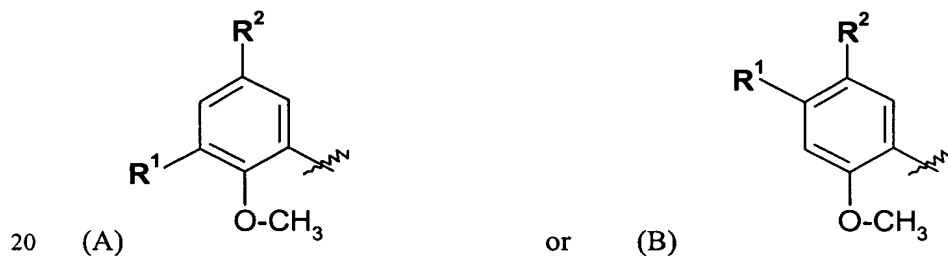
a bond, -O-, -O-(CH₂)₁₋₅-, -NH-, -C(O)-NH-, C₁₋₅ alkyl branched or unbranched, C₂₋₅ alkenyl, C₁₋₃ alkyl(OH), heterocycle selected from morpholinyl, piperazinyl, piperidinyl and pyrrolidinyl or phenyl, each alkyl, alkenyl, heterocycle and phenyl are optionally substituted by one to three hydroxy, C₁₋₃ alkyl, C₁₋₃ alkoxy, mono or diC₁₋₃ alkyl amino, amino or C₁₋₅ alkoxycarbonyl;

wherein each **R**₆ is further optionally covalently attached to groups chosen from:

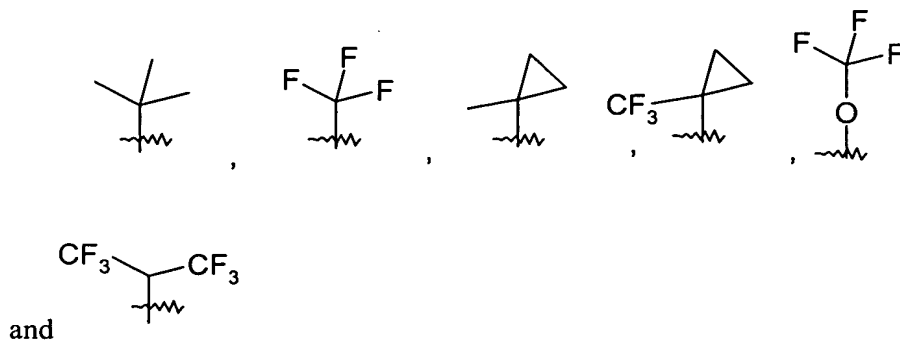
hydrogen, -NR₇R₈, C₁₋₃ alkyl, C₃₋₆ cycloalkylC₀₋₂alkyl, benzyloxy, phenylC₀₋₄ alkyl, piperazinyl, piperazinylC₁₋₂ alkyl, piperidinyl, piperidinyl C₁₋₂alkyl, pyrrolidinyl, pyrrolidinyl C₁₋₂ alkyl, morpholinyl, morpholinylC₁₋₂ alkyl, triazolyl, triazolyl C₁₋₂alkyl, imidazolyl, imidazolyl C₁₋₂alkyl, pyridinyl and pyridinyl C₁₋₂alkyl, each above-listed heterocycle, heteroaryl and phenyl group is optionally substituted by one to three hydroxy, oxo, C₁₋₄ alkyl, C₁₋₃ alkoxy, C₁₋₅ alkoxycarbonyl, amino, NR₇R₈-C(O)- or C₁₋₄ acyl.

In yet still another embodiment, there are provided compounds of the formula (I) as described immediately above and wherein

Ar¹ is formula (A) or (B)



and **R**² is chosen from



when Ar^1 is formula (A) then:

when R^1 is $\text{J-S(O)}_2\text{-N(R}^a\text{)-}$ or $\text{J-N(R}^a\text{)-S(O)}_2\text{-}$ then J is C_{1-3} alkyl;

and

- 5 when R^1 is NH_2 , $\text{J-N(R}^a\text{)-(CH}_2\text{)}_m\text{-}$, $\text{NH}_2\text{C(O)-}$, $\text{J-N(R}^a\text{)-C(O)-}$, or heterocycle- $(\text{CH}_2)_{1-2}\text{-}$ wherein the heterocycle is chosen from pyrrolidinyl, morpholinyl, piperazinyl or C1-4alkylpiperazinyl, then
 J is C1-3 alkyl optionally substituted by R^b .

10

In yet another embodiment, there are provided compounds of the formula (I) as described immediately above and wherein

- R^b is chosen from hydrogen, C1-5 alkyl, C3-6 cycloalkyl, C0-2 alkyl, phenyl, C1-5
 15 alkoxy, amino, C1-5 alkylamino, C1-3 dialkylamino, C1-3 acyl, C1-5 alkoxycarbonyl, C1-3 acyloxy, C1-3 acylamino, hydroxy, halogen;
 or R^b is chosen from morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, piperidinyl, piperidinonyl, pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl.

20

In yet another embodiment, there are provided compounds of the formula (I) as described immediately above and wherein

- R^b is chosen from amino, C1-5 alkylamino, C1-3 dialkylamino;
 25 or R^b is chosen morpholinyl, piperidinyl and pyridinyl.

In yet still another embodiment, there are provided compounds of the formula (I) as described immediately above and wherein

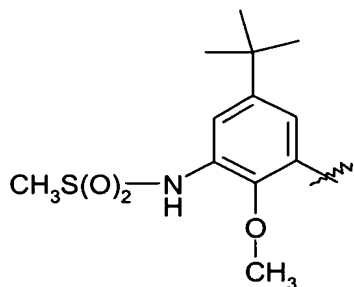
- 30 Ar^1 is formula (A).

In yet still another embodiment, there are provided compounds of the formula (I) as described above and wherein

Ar^1 is formula (B).

- 5 In yet another embodiment, there are provided compounds of the formula (I) as described above and wherein

Ar^1 is



10

The following are representative compounds of the invention which have been made according to the general schemes and working examples below:

Table I

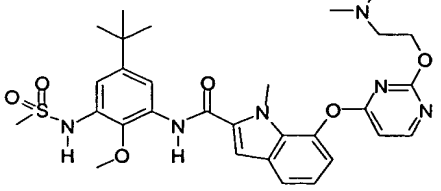
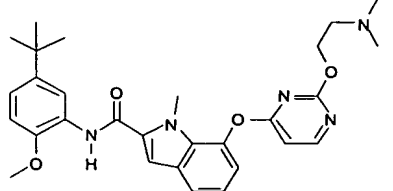
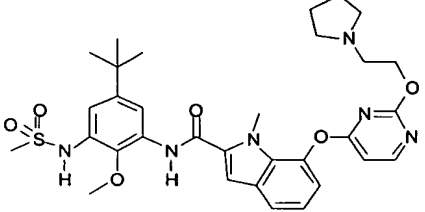
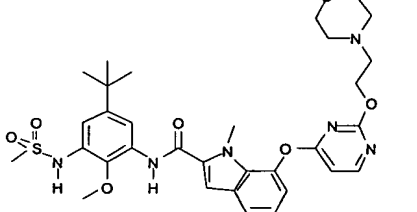
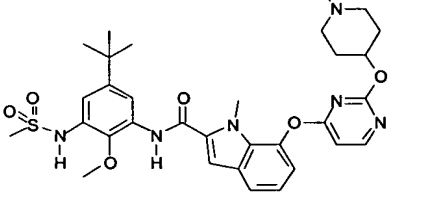
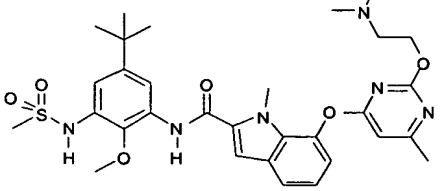
15

	<p>1-Methyl-7-(pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide</p>
	<p>7-(2-Methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide</p>

	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-2-methoxy-phenyl)-amide
	7-[2-(2-Dimethylamino-ethylamino)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-(2-Cyclopropylamino-pyrimidin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(4-Methoxy-benzylamino)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

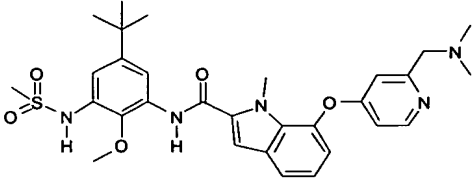
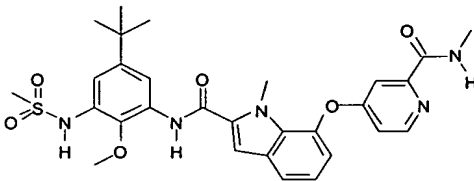
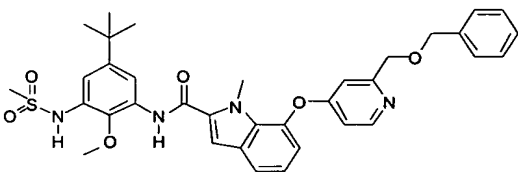
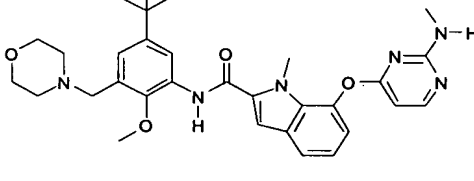
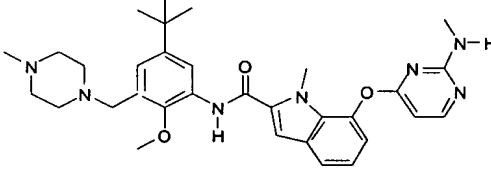
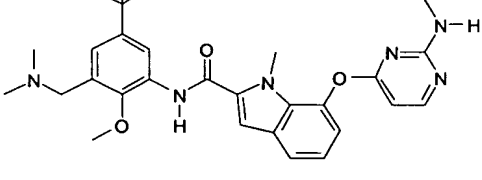
	7-[2-(2-Dimethylamino-ethylamino)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(3-Dimethylamino-propylamino)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(3-Dimethylamino-2,2-dimethyl-propylamino)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-(2-Dimethylamino-pyrimidin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

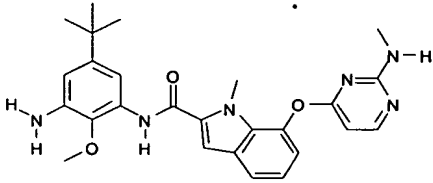
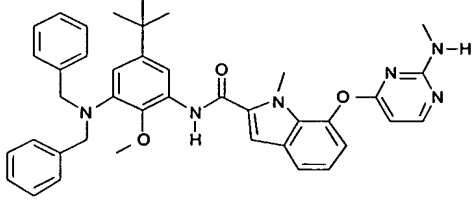
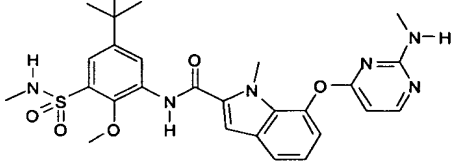
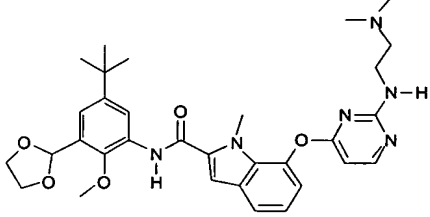
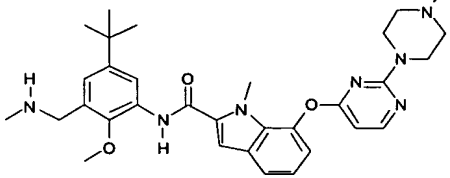
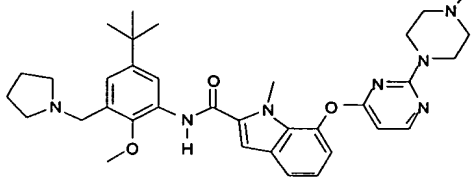
	1-Methyl-7-(6-methyl-2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(2-pyrrolidin-1-yl-ethylamino)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(piperidin-4-ylamino)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	4-{4-[2-(5-tert-Butyl-3-methanesulfonylamino-2-methoxy-phenylcarbamoyl)-1-methyl-1H-indol-7-yloxy]-pyrimidin-2-ylamino}-piperidine-1-carboxylic acid tert-butyl ester
	7-{2-[(2-Dimethylamino-ethyl)-methylamino]-pyrimidin-4-yloxy}-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[6-methyl-2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

	7-[2-(2-Dimethylamino-ethoxy)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(2-Dimethylamino-ethoxy)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(2-pyrrolidin-1-yl-ethoxy)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(2-morpholin-4-yl-ethoxy)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(1-methyl-piperidin-4-yloxy)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(2-Dimethylamino-ethoxy)-6-methyl-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

	1-Methyl-7-(2-methylcarbamoyl-pyridin-4-yloxy)-1H-indole-2-carboxylic acid [5-tert-butyl-3-(2-dimethylamino-ethylcarbamoyl)-2-methoxy-phenyl]-amide
	7-[2-(2-Dimethylamino-ethylcarbamoyl)-pyridin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid [5-tert-butyl-3-(2-dimethylamino-ethylcarbamoyl)-2-methoxy-phenyl]-amide
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid [5-tert-butyl-2-methoxy-3-(2-morpholin-4-ylethylcarbamoyl)-phenyl]-amide
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-carbamoyl-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-2-methoxy-3-methylcarbamoyl-phenyl)-amide

	1-Methyl-7-(2-vinyl-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(1,2-Dihydroxy-ethyl)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(morpholin-4-ylamino)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-morpholin-4-ylmethyl-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-morpholin-4-ylmethyl-pyridin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(4-methyl-piperazin-1-ylmethyl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

	7-(2-Dimethylaminomethyl-pyridin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-methylcarbamoyl-pyridin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-(2-Benzoyloxymethyl-pyridin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-2-methoxy-3-morpholin-4-ylmethyl-phenyl)-amide
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid [5-tert-butyl-2-methoxy-3-(4-methylpiperazin-1-ylmethyl)-phenyl]-amide
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-dimethylaminomethyl-2-methoxy-phenyl)-amide

	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (3-amino-5-tert-butyl-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-dibenzylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-2-methoxy-3-methylsulfamoyl-phenyl)-amide
	7-[2-(2-Dimethylamino-ethylamino)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-[1,3]dioxolan-2-yl-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-2-methoxy-3-methylaminomethyl-phenyl)-amide
	1-Methyl-7-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-2-methoxy-3-pyrrolidin-1-ylmethyl-phenyl)-amide

	1-Methyl-7-{2-[methyl-(1-methyl-piperidin-4-yl)-amino]-pyrimidin-4-yloxy}-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-(2-Hydroxymethyl-pyridin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide and
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid [5-tert-butyl-2-methoxy-3-(2-morpholin-4-yl-ethylamino)-phenyl]-amide
	1-Methyl-7-(pyridin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-piperazin-1-yl-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid [3-methanesulfonylamino-2-methoxy-5-(1-methyl-cyclopropyl)-phenyl]-amide

	1-Methyl-7-[2-(5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(2,5-Diaza-bicyclo[2.2.1]hept-2-yl)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-(2-Methoxy-pyrimidin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(4-tert-Butyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(2-morpholin-4-yl-ethyl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-{2-[2-(4-methyl-piperazin-1-yl)-ethyl]-pyrimidin-4-yloxy}-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

	1-Methyl-7-[2-(2-pyrrolidin-1-yl-ethyl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(2-Dimethylamino-ethyl)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(2-morpholin-4-yl-ethyl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (3-methanesulfonylamino-2-methoxy-5-trifluoromethyl-phenyl)-amide
	1-Methyl-7-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (3-methanesulfonylamino-2-methoxy-5-trifluoromethyl-phenyl)-amide
	7-{2-[2-(4-tert-Butyl-piperazin-1-yl)-ethyl]-pyrimidin-4-yloxy}-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(4-tert-Butyl-piperazin-1-ylmethyl)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

	1-Methyl-7-(2-pyrrolidin-1-ylmethyl-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-(2,6-Dimethyl-pyridin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-(2-Ethyl-pyridin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(1,2,3,6-tetrahydro-pyridin-4-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-(2-Amino-pyrimidin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-pyrrolidin-1-ylmethyl-pyridin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

	1-Methyl-7-(2-piperidin-1-ylmethyl-pyridin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(4-methyl-piperazin-1-ylmethyl)-pyridin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(pyridin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-[(2-dimethylamino-ethyl)-methyl-amino]-methyl}-2-methoxy-phenyl)-amide
	7-(2-[(2-Dimethylamino-ethyl)-methyl-amino]-methyl}-pyrimidin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-carbamoyl-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-((1S,4S)-5-methyl-2,5-diaza-bicyclo[2.2.1]hept-2-yl)-pyridin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

	1-Methyl-7-[2-(4-methyl-[1,4]diazepan-1-yl)-pyridin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-(2-[1,4]Diazepan-1-yl-pyridin-4-yloxy)-1-methyl-1-H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-piperazin-1-yl-pyridin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-trideuterio-7-(2-piperazin-1-yl-pyridin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(Hexahydro-pyrrolo[1,2-a]pyrazin-2-yl)-pyridin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-trideuterio-7-[2-(4-methyl-piperazin-1-yl)-pyridin-4-yloxy]-1H-indole-2-carboxylic acid [3-methanesulfonylamino-2-methoxy-5-(1-methyl-cyclopropyl)-phenyl]-amide

	7-[2-((S)-3-Dimethylamino-pyrrolidin-1-yl)-pyridin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid [3-methanesulfonylamino-2-methoxy-5-(1-methyl-cyclopropyl)-phenyl]-amide
	7-[2-((S)-3-Dimethylamino-pyrrolidin-1-yl)-pyridin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid [3-methanesulfonylamino-2-methoxy-5-(1-methyl-cyclopropyl)-phenyl]-amide
	1-Methyl-7-[2-(4-methyl-piperazine-1-carbonyl)-pyridin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(piperazine-1-carbonyl)-pyridin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

or the pharmaceutically acceptable salts, acids, esters or isomers thereof.

5

Preferred compounds of the invention are listed in table II.

Table II

	1-Methyl-7-(pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
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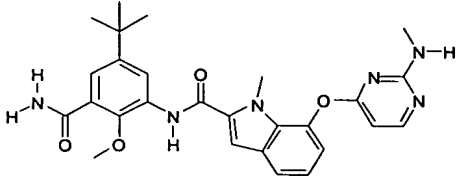
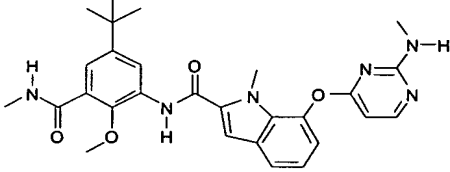
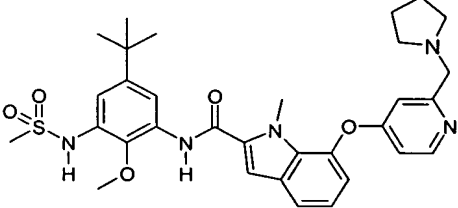
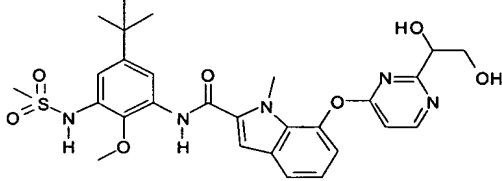
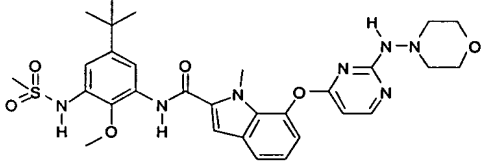
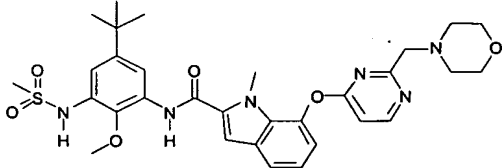
	1-Methyl-7-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-carbamoyl-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-pyrrolidin-1-ylmethyl-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-(2-[(2-Dimethylamino-ethyl)-methyl-amino]-methyl)-pyrimidin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(pyridin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-[(2-dimethylamino-ethyl)-methyl-amino]-methyl}-2-methoxy-phenyl)-amide
	7-[2-(4-tert-Butyl-piperazin-1-ylmethyl)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-(2-Dimethylaminomethyl-pyridin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

	7-{2-[2-(4-tert-Butyl-piperazin-1-yl)-ethyl]-pyrimidin-4-yloxy}-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(2-pyrrolidin-1-yl-ethyl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(2-Dimethylamino-ethylamino)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(2-morpholin-4-yl-ethyl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

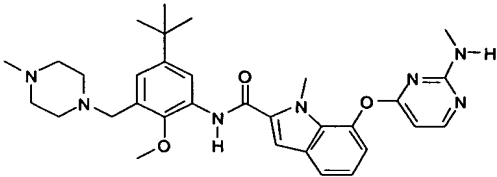
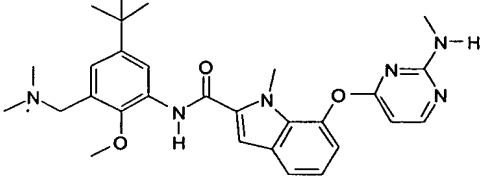
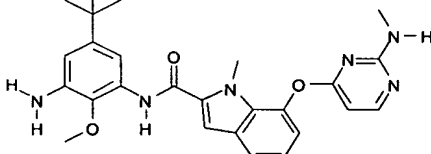
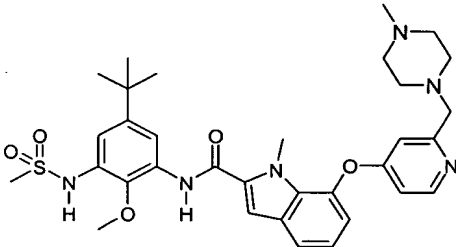
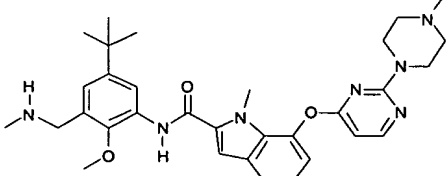
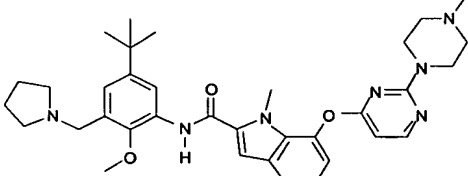
	1-Methyl-7-[2-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(3-Dimethylamino-propylamino)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(3-Dimethylamino-2,2-dimethyl-propylamino)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-(2-Dimethylamino-pyrimidin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(6-methyl-2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(2-pyrrolidin-1-yl-ethylamino)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

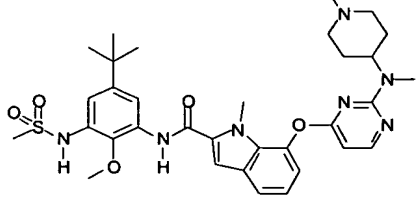
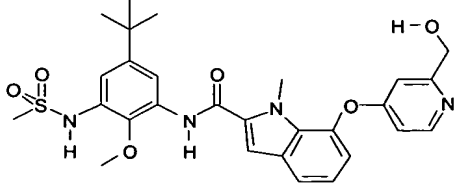
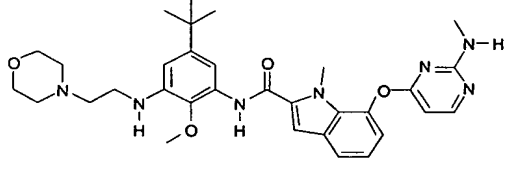
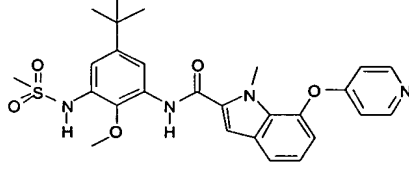
	1-Methyl-7-[2-(piperidin-4-ylamino)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-pyrimidin-4-yloxy}-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-{2-[2-(4-methyl-piperazin-1-yl)-ethyl]-pyrimidin-4-yloxy}-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(2-Dimethylamino-ethoxy)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(2-pyrrolidin-1-yl)-ethoxy]-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(2-morpholin-4-yl)-ethoxy]-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

	1-Methyl-7-[2-(1-methyl-piperidin-4-yloxy)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(4-tert-Butyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-methylcarbamoyl-pyridin-4-yloxy)-1H-indole-2-carboxylic acid [5-tert-butyl-3-(2-dimethylamino-ethylcarbamoyl)-2-methoxy-phenyl]-amide
	7-[2-(2-Dimethylamino-ethylcarbamoyl)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid [5-tert-butyl-3-(2-dimethylamino-ethylcarbamoyl)-2-methoxy-phenyl]-amide
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid [5-tert-butyl-2-methoxy-3-(2-morpholin-4-ylethylcarbamoyl)-phenyl]-amide

	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-carbamoyl-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-2-methoxy-3-methylcarbamoyl-phenyl)-amide
	1-Methyl-7-(2-pyrrolidin-1-ylmethyl-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(1,2-Dihydroxy-ethyl)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(morpholin-4-ylamino)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-morpholin-4-ylmethyl-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

	1-Methyl-7-(2-morpholin-4-ylmethyl-pyridin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(4-methyl-piperazin-1-ylmethyl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-(2-Dimethylaminomethyl-pyridin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-methylcarbamoyl-pyridin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-piperidin-1-ylmethyl-pyridin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-2-methoxy-3-morpholin-4-ylmethyl-phenyl)-amide

	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid [5-tert-butyl-2-methoxy-3-(4-methyl-piperazin-1-ylmethyl)-phenyl]-amide
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-dimethylaminomethyl-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (3-amino-5-tert-butyl-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(4-methyl-piperazin-1-ylmethyl)-pyridin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-2-methoxy-3-methylaminomethyl-phenyl)-amide
	1-Methyl-7-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-2-methoxy-3-pyrrolidin-1-ylmethyl-phenyl)-amide

	1-Methyl-7-{2-[methyl-(1-methyl-piperidin-4-yl)-amino]-pyrimidin-4-yloxy}-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-(2-Hydroxymethyl-pyridin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid [5-tert-butyl-2-methoxy-3-(2-morpholin-4-ylethylamino)-phenyl]-amide and
	1-Methyl-7-(pyridin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

or the pharmaceutically acceptable salts, acids, esters or isomers thereof.

5

The following are representative compounds of the invention which can be made according to the general schemes and working examples below:

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Table III

	7-(Pyrimidin-4-yloxy)-benzo[b]thiophene-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-(Pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-(Pyrimidin-4-yloxy)-benzofuran-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(pyrimidin-4-ylsulfanyl)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(pyrimidin-4-ylamino)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(pyridin-3-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

	7-(2-Benzylamino-pyrimidin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-{2-[(pyridin-2-ylmethyl)-amino]-pyrimidin-4-yloxy}-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(2-Imidazol-1-yl-ethylamino)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(2-[1,2,3]triazol-1-yl-ethylamino)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(3-Dimethylamino-propylamino)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid [2-methoxy-5-(2,2,2-trifluoro-1-trifluoromethyl-ethyl)-phenyl]-amide
	7-{2-[(2-Dimethylamino-ethyl)-methylamino]-pyrimidin-4-yloxy}-1-methyl-1H-indole-2-carboxylic acid (4-chloro-2-methoxy-5-trifluoromethyl-phenyl)-amide

	7-[2-(4-Acetyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (4-chloro-2-methoxy-5-trifluoromethyl-phenyl)-amide
	7-[2-(2-Dimethylamino-ethylamino)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (2-methoxy-5-trifluoromethoxy-phenyl)-amide
	7-[2-(4-Dimethylamino-piperidin-1-yl)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(3-Dimethylamino-pyrrolidin-1-yl)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(1-methyl-piperidin-4-ylamino)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

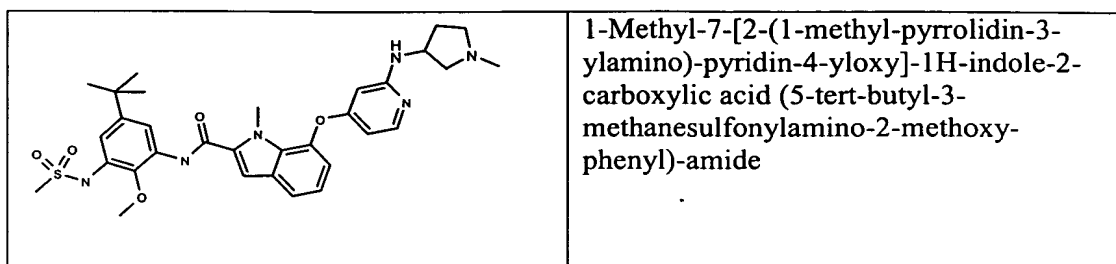
	7-[2-(1-Acetyl-piperidin-4-ylamino)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(2-morpholin-4-yl-ethoxy)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (3-methanesulfonylamino-2-methoxy-5-trifluoromethyl-phenyl)-amide
	7-[2-(2-Imidazol-1-yl-ethoxy)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(2-Imidazol-1-yl-ethoxy)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (4-chloro-2-methoxy-5-trifluoromethyl-phenyl)-amide
	7-[2-(2-Dimethylamino-ethylamino)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-2-methoxy-3-methylcarbamoyl-phenyl)-amide
	7-(2-Amino-pyrimidin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-carbamoyl-2-methoxy-phenyl)-amide

	7-(2-Amino-pyrimidin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid [5-tert-butyl-3-(2-dimethylamino-ethylcarbamoyl)-2-methoxy-phenyl]-amide
	7-[2-(2-Dimethylamino-ethylamino)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-dimethylaminomethyl-2-methoxy-phenyl)-amide
	7-[2-(2-Dimethylamino-ethylamino)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-2-methoxy-3-pyrrolidin-1-ylmethyl-phenyl)-amide
	7-[2-(2-Dimethylamino-ethylamino)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-2-methoxy-3-morpholin-4-ylmethyl-phenyl)-amide
	1-Methyl-7-(2-morpholin-4-ylmethyl-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (4-chloro-2-methoxy-5-trifluoromethyl-phenyl)-amide
	7-[2-(3-Dimethylamino-pyrrolidin-1-ylmethyl)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

	7-(2-Carbamoyl-pyrimidin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-(2-morpholin-4-ylmethyl-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (2-methoxy-3-morpholin-4-ylmethyl-5-trifluoromethyl-phenyl)-amide
	1-Methyl-7-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (2-methoxy-3-morpholin-4-ylmethyl-5-trifluoromethyl-phenyl)-amide
	1-Methyl-7-(2-morpholin-4-ylmethyl-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (3-methanesulfonylamino-2-methoxy-5-trifluoromethyl-phenyl)-amide
	7-(1'-tert-Butyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (3-methanesulfonylamino-2-methoxy-5-trifluoromethyl-phenyl)-amide
	1-Methyl-7-(2-methylaminomethyl-pyridin-4-yloxy)-1H-indole-2-carboxylic acid (3-methanesulfonylamino-2-methoxy-5-trifluoromethyl-phenyl)-amide

	1-Methyl-7-(2-pyrrolidin-1-ylmethyl-pyridin-4-yloxy)-1H-indole-2-carboxylic acid (2-methoxy-3-morpholin-4-ylmethyl-5-trifluoromethyl-phenyl)-amide
	1-Methyl-7-[2-(2-morpholin-4-yl-ethyl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (3-dimethylaminomethyl-2-methoxy-5-trifluoromethyl-phenyl)-amide
	1-Methyl-7-(2-pyrrolidin-1-ylmethyl-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (2-methoxy-3-pyrrolidin-1-ylmethyl-5-trifluoromethyl-phenyl)-amide
	7-(2-Dimethylaminomethyl-pyrimidin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid [2-methoxy-3-(4-methyl-piperazin-1-ylmethyl)-5-trifluoromethyl-phenyl]-amide
	7-(2-Dimethylaminomethyl-pyridin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (3-methanesulfonylamino-2-methoxy-5-trifluoromethyl-phenyl)-amide
	7-(2-Dimethylaminomethyl-pyrimidin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (3-methanesulfonylamino-2-methoxy-5-trifluoromethyl-phenyl)-amide

	1-Methyl-7-[2-(4-methyl-piperazin-1-ylmethyl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (3-methanesulfonylamino-2-methoxy-5-trifluoromethyl-phenyl)-amide
	7-(2-Dimethylaminomethyl-pyrimidin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (3-methanesulfonylamino-2-methoxy-5-trifluoromethyl-phenyl)-amide
	1-Methyl-7-[2-(2-morpholin-4-yl-ethyl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid [3-methanesulfonylamino-2-methoxy-5-(1-methyl-cyclopropyl)-phenyl]-amide
	1-Methyl-7-[2-(1-methyl-piperidin-4-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	7-[2-(1-Cyclopropyl-piperidin-4-yl)-pyrimidin-4-yloxy]-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide
	1-Methyl-7-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (3-dimethylaminomethyl-2-methoxy-5-trifluoromethyl-phenyl)-amide



or the pharmaceutically acceptable salts, acids, esters or isomers thereof.

5

In all the compounds disclosed hereinabove in this application, in the event the nomenclature is in conflict with the structure, it shall be understood that the compound is defined by the structure.

- 10 Of particular importance according to the invention are compounds of formula (I), wherein Ar_1 , X , Y , Q , W , R^3 , R^4 , R^5 , R^6 and R^y have the meaning indicated, for use as pharmaceutical compositions with an anti-cytokine activity.

- The invention also relates to the use of a compound of formula (I), wherein Ar_1 , X , Y , Q , W , R^3 , R^4 , R^5 , R^6 and R^y have the meaning indicated, for preparing a
15 pharmaceutical composition for the treatment and/or prevention of a cytokine mediated disease or condition..

- The invention also relates to pharmaceutical preparations, containing as active
20 substance one or more compounds of formula (I), wherein Ar_1 , X , Y , Q , W , R^3 , R^4 , R^5 , R^6 and R^y have the meanings indicated, or the pharmaceutically acceptable derivatives thereof, optionally combined with conventional excipients and/or carriers.

- Compounds of the invention also include their isotopically-labelled forms. An
25 isotopically-labelled form of an active agent of a combination of the present invention is identical to said active agent but for the fact that one or more atoms of said active agent have been replaced by an atom or atoms having an atomic mass or mass number different from the atomic mass or mass number of said atom which is usually found in nature. Examples of isotopes which are readily available commercially and which can

be incorporated into an active agent of a combination of the present invention in accordance with well established procedures, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, *e.g.*, ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. An active agent of a combination of the present invention, a prodrug thereof, or a pharmaceutically acceptable salt of either which contains one or more of the above-mentioned isotopes and/or other isotopes of other atoms is contemplated to be within the scope of the present invention.

The invention includes the use of any compounds of described above containing one or more asymmetric carbon atoms may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be in the R or S configuration, or a combination of configurations.

Some of the compounds of formula (I) can exist in more than one tautomeric form. The invention includes methods using all such tautomers.

All terms as used herein in this specification, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. For example, "C₁₋₄alkoxy" is a C₁₋₄alkyl with a terminal oxygen, such as methoxy, ethoxy, propoxy, butoxy. All alkyl, alkenyl and alkynyl groups shall be understood as being branched or unbranched where structurally possible and unless otherwise specified. Other more specific definitions are as follows:

The term "aroyl" as used in the present specification shall be understood to mean "benzoyl" or "naphthoyl".

Carbocycles include hydrocarbon rings containing from three to twelve carbon atoms. These carbocycles may be either aromatic or non-aromatic ring systems. The non-aromatic ring systems may be mono- or polyunsaturated. Preferred carbocycles include but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptanyl, cycloheptenyl, phenyl, indanyl, indenyl, benzocyclobutanyl, dihydronaphthyl, tetrahydronaphthyl, naphthyl,

decahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl. Certain terms for cycloalkyl such as cyclobutanyl and cyclobutyl shall be used interchangeably.

The term "heterocycle" refers to a stable nonaromatic 4-8 membered (but preferably, 5 or 6 membered) monocyclic or nonaromatic 8-11 membered bicyclic heterocycle radical which may be either saturated or unsaturated. Each heterocycle consists of carbon atoms and one or more, preferably from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be attached by any atom of the cycle, which results in the creation of a stable structure. Unless otherwise stated, heterocycles include but are not limited to, for example pyrrolidinyl, pyrrolinyl, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, dioxalanyl, piperidinyl, piperazinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxanyl, piperidinonyl, tetrahydropyrimidinyl, pentamethylene sulfide, pentamethylene sulfoxide, pentamethylene sulfone, tetramethylene sulfide, tetramethylene sulfoxide and tetramethylene sulfone.

The term "heteroaryl" shall be understood to mean an aromatic 5-8 membered monocyclic or 8-11 membered bicyclic ring containing 1-4 heteroatoms such as N, O and S. Unless otherwise stated, such heteroaryls include aziridinyl, thienyl, furanyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl, tetrazolyl, pyrazolyl, pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyranyl, quinoxalinyl, indolyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, benzothieryl, quinolinyl, quinazolinyl, naphthyridinyl, indazolyl, triazolyl, pyrazolo[3,4-*b*]pyrimidinyl, purinyl, pyrrolo[2,3-*b*]pyridinyl, pyrazolo[3,4-*b*]pyridinyl, tubercidinyl, oxazo[4,5-*b*]pyridinyl and imidazo[4,5-*b*]pyridinyl.

The term "heteroatom" as used herein shall be understood to mean atoms other than carbon such as O, N, S and P.

In all alkyl groups or carbon chains one or more carbon atoms can be optionally replaced by heteroatoms: O, S or N, it shall be understood that if N is not substituted then it is NH, it shall also be understood that the heteroatoms may replace either terminal carbon atoms or internal carbon atoms within a branched or unbranched carbon chain. Such groups can be substituted as herein above described by groups such as oxo

to result in definitions such as but not limited to: alkoxycarbonyl, acyl, amido and thioxo.

The term "aryl" as used herein shall be understood to mean aromatic carbocycle or heteroaryl as defined herein. Each aryl or heteroaryl unless otherwise specified includes its partially or fully hydrogenated derivative. For example, quinolinyl may include decahydroquinolinyl and tetrahydroquinolinyl, naphthyl may include its hydrogenated derivatives such as tetrahydronaphthyl. Other partially or fully hydrogenated derivatives of the aryl and heteroaryl compounds described herein will be apparent to one of ordinary skill in the art.

As used herein, "nitrogen" and "sulfur" include any oxidized form of nitrogen and sulfur and the quaternized form of any basic nitrogen. For example, for an $-S-C_{1-6}$ alkyl radical, unless otherwise specified, this shall be understood to include $-S(O)-C_{1-6}$ alkyl and $-S(O)_2-C_{1-6}$ alkyl.

The term "halogen" as used in the present specification shall be understood to mean bromine, chlorine, fluorine or iodine, preferably fluorine. The definitions "partially or fully halogenated"; partially or fully fluorinated; "substituted by one or more halogen atoms", includes for example, mono, di or tri halo derivatives on one or more carbon atoms. For alkyl, a nonlimiting example would be $-CH_2CHF_2$, $-CF_3$ etc.

The compounds of the invention are only those which are contemplated to be 'chemically stable' as will be appreciated by those skilled in the art. For example, a compound which would have a 'dangling valency', or a 'carbanion' are not compounds contemplated by the inventive methods disclosed herein.

The invention includes pharmaceutically acceptable derivatives of compounds of formula (I). A "pharmaceutically acceptable derivative" refers to any pharmaceutically acceptable salt or ester, or any other compound which, upon administration to a patient, is capable of providing (directly or indirectly) a compound useful for the invention, or a pharmacologically active metabolite or pharmacologically active residue thereof. A pharmacologically active metabolite shall be understood to mean any compound of the

invention capable of being metabolized enzymatically or chemically. This includes, for example, hydroxylated or oxidized derivative compounds of the formula (I).

- Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfuric, tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfuric and benzenesulfonic acids. Other acids, such as oxalic acid, while not themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (*e.g.*, sodium), alkaline earth metal (*e.g.*, magnesium), ammonium and N-(C₁-C₄ alkyl)₄⁺ salts.
- In addition, within the scope of the invention is use of prodrugs of compounds of the formula (I). Prodrugs include those compounds that, upon simple chemical transformation, are modified to produce compounds of the invention. Simple chemical transformations include hydrolysis, oxidation and reduction. Specifically, when a prodrug is administered to a patient, the prodrug may be transformed into a compound disclosed hereinabove, thereby imparting the desired pharmacological effect.

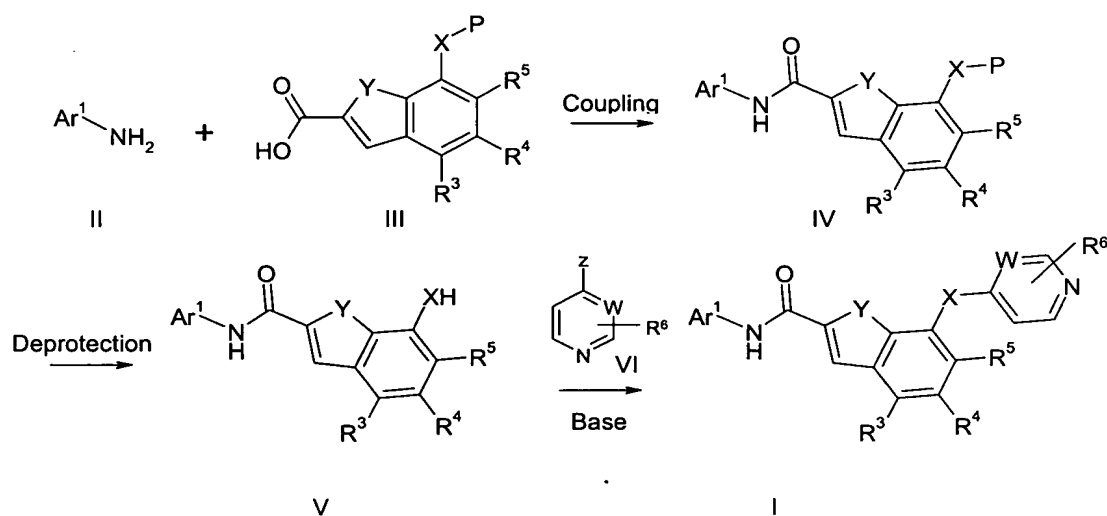
GENERAL SYNTHETIC METHODS

- The invention additionally provides for methods of making the compounds of the formula (I). The compounds of the invention may be prepared by the general methods and examples presented below, and methods known to those of ordinary skill in the art. Further reference in this regard may be made to US patent no. 6,358,945, US application nos. 09/714,539, 09/834,797, 10/120,028, 10/143,322 and 10/147,675. US application no. 10/264,689 teaches additional methods for preparation of sulfonamide intermediates. Each of the aforementioned US cases are incorporated in their entirety. In all schemes, unless otherwise specified, Ar¹, X, Y, W and R³-R⁶ in the formulas shown below shall have the meanings defined for these groups in the definition of the

formula (I) of the invention, described hereinabove. Intermediates used in the syntheses below are either commercially available or easily prepared by methods known to those skilled in the art. Reaction progress may be monitored by conventional methods such as thin layer chromatography (TLC). Intermediates and products may be purified by methods known in the art, including column chromatography, HPLC or recrystallization.

Compounds of the invention where Q is a carbon atom, may be prepared as described in Schemes I and II. Compounds of the invention wherein Q is a nitrogen atom, may be prepared by analogous methods which will be apparent to one of ordinary skill in the art.

Scheme I



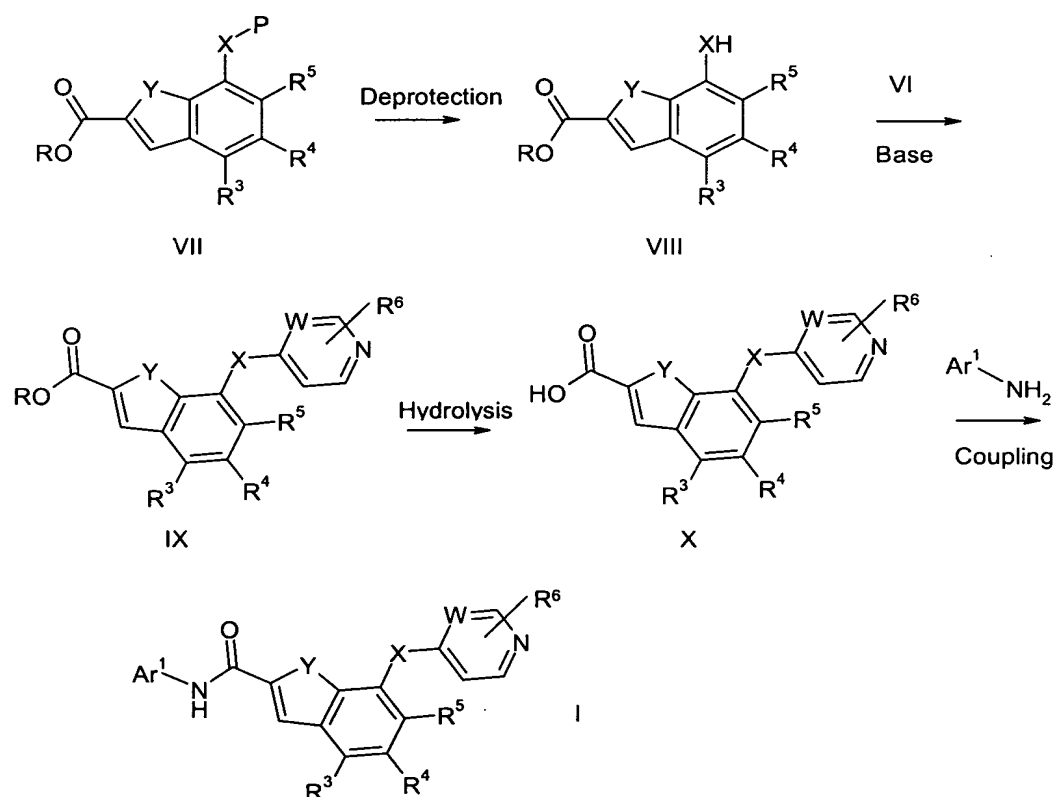
As illustrated in Scheme I an amine bearing Ar¹ is coupled with carboxylic acid III, where P is a protecting group, using standard coupling conditions known in the art (see for example M. Bodanszky, 1984, *The Practice of Peptide Synthesis*, Springer-Verlag). For example, one may couple III and II by treating with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) followed by 1-hydroxybenzotriazole hydrate (HOBT) in a suitable solvent such as DMF. Removal of the protecting group P to provide V may be achieved by standard procedures known in the art. For example, if P is a benzyl group, it may be removed by treatment of IV with hydrogen gas in the

presence of a catalyst such as palladium on carbon in a suitable solvent such as EtOH .
 The resulting intermediate V may then be coupled with the desired halo heterocycle VI
 (Z = halogen) bearing R⁶ in the presence of a suitable base to provide I. Ar¹ and R⁶ may
 be further modified by standard synthetic methods known in the art to produce
 5 additional compounds of formula (I). Several examples are described in the Synthetic
 Examples section below.

In a modification of the above method, the order of coupling VI and Ar¹NH₂ with the
 central heterocycle may be reversed. This is illustrated in Scheme II.

10

Scheme II



15 As illustrated above, the ester VII (R = lower alkyl such as methyl or ethyl, P = a
 protecting group) is deprotected as described above and the resulting intermediate VIII
 is coupled, as described above to provide ester IX. This is hydrolyzed using standard
 hydrolysis conditions and the resulting acid coupled with Ar¹NH₂ to provide I. As

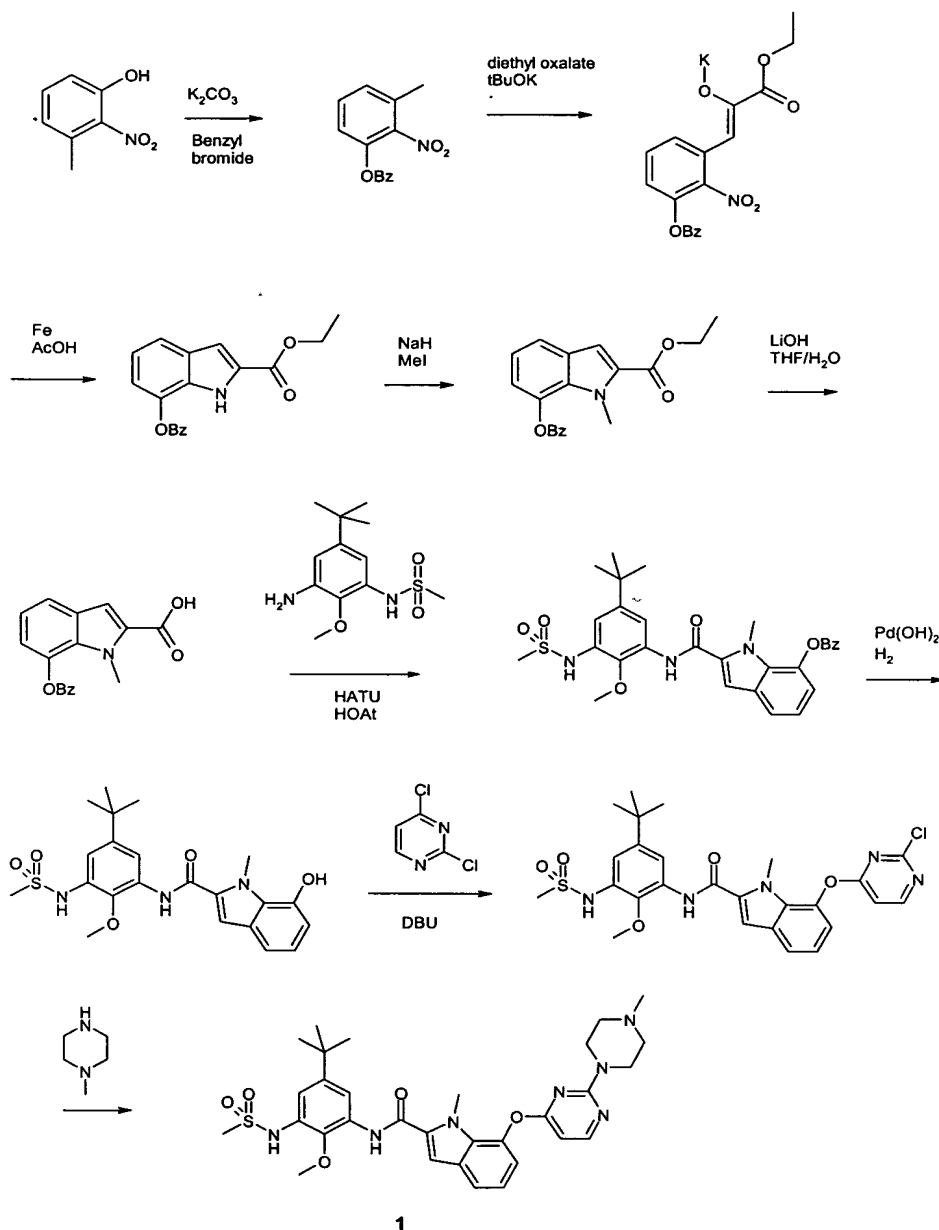
above, Ar¹ and R⁶ may be further modified by standard synthetic methods known in the art to produce additional compounds of formula (I). Several examples are described in the Synthetic Examples section below. .

5

SYNTHETIC EXAMPLES

Example 1: Synthesis of 1-methyl-7-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

10



For a similar procedure to form the indole core, see R. Albrecht et al. *Eur. J. Med. Chem. Chim. Ther.* **1985**, *20*, 59-60.

- 5 In a 1 L 3-neck round-bottom flask equipped with a condenser and mechanical stirrer were placed the 2-nitro-3-methylphenol (50.8 g, 331.5 mmol), 500 mL anhydrous acetonitrile and potassium carbonate (57.3 g, 414.3 mmol). The yellow solution became orange. While stirring, benzyl bromide (39.4 mL, 331.5 mmol) was added slowly *via* syringe, then the mixture was heated to gentle reflux overnight and allowed to cool. An

orange precipitates formed. The reaction was quenched with water and extracted with EtOAc three times. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The desired benzyl ether was obtained as a yellow oil, 80.7 g (quantitative).

5

Potassium *tert*-Butoxide solution (1.0 M in THF, 100 mL, 100 mmol) was placed in a 1000 mL round-bottom flask under inert atmosphere. Ether (370 mL) was then added causing the solution to become murky. This was followed by addition of diethyl oxalate (14.0 mL, 103.1 mmol). The solution became yellow. After stirring 10 min, the benzyl ether from above (24.3 g, 99.9 mmol) was added directly to the flask and the mixture was left standing overnight. The reaction was heated to a gentle reflux for 18 h then left at room temperature overnight. An orange precipitate had formed. The precipitated product was filtered through a Buchner funnel and washed ether providing 29.1 g of the desired condensation product as the potassium salt.

15

In a 1 L 3-neck round-bottom flask equipped with a condenser and mechanical stirrer were placed the potassium salt from above (29.1 g, 76.3 mmol) and 250 mL glacial acetic acid. Iron powder (25.6 g, 458.0 mmol) was added and the reaction was stirred at 100 °C for 1 h and then allowed to cool. EtOAc (800 mL) was added and the mixture was filtered through diatomaceous earth and left standing overnight. A saturated aqueous solution of NaHCO_3 was added slowly to the filtrate. A lot of bubbling was observed. The layers were separated and the organic phase was washed with water and brine, dried (MgSO_4), filtered and concentrated *in vacuo*. The resulting product was dried under high vacuum overnight. It was then decolorized with charcoal by heating in an EtOH/MeOH mixture, filtered and concentrated *in vacuo*, providing 7.5 g of the desired indole ester.

20

The indole ester (19.0 g, 64.3 mmol) was dissolved in 160 mL anhydrous DMF at room temperature and treated with sodium hydride (4.0 g, 100 mmol), added portionwise.

30

Once the mixture cooled back to room temperature, iodomethane (6.2 mL, 100 mmol) was added. Vigorous heating was again observed. One extra equivalent of iodomethane was added. The mixture was left stirring overnight and was then partitioned between EtOAc and saturated aqueous ammonium chloride solution. The

organic phase was washed with water twice, then brine, dried (MgSO_4), filtered and concentrated *in vacuo* leaving a brown oil. The product was purified by column chromatography on SiO_2 using 10, 20 % EtOAc in hexanes as eluent. The 1-methyl indole ester (17.2 g, mixture of methyl and ethyl esters) was isolated as a pale yellow solid.

The above ester (4.01 g, 13.0 mmol) was placed in 100 mL THF and treated with LiOH hydrate (1.1 g, 26.0 mmol) dissolved in 15 mL water. The resulting slightly murky solution was left stirring vigorously at room temperature for 3 days. It was then acidified with dilute aqueous HCl to pH \sim 1 and extracted with EtOAc twice. The extracts were washed with brine twice and dried (MgSO_4), filtered and concentrated *in vacuo*. The resulting carboxylic acid (3.75 g, quantitative) was obtained as a white solid.

The carboxylic acid (0.93 g, 3.31 mmol) in 10 mL anhydrous DMF at room temperature under N_2 was treated with O-(7-azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium hexafluorophosphate (HATU) (1.71 g, 4.50 mmol), triethylamine (1.75 mL, 12.57 mmol) and catalytic 1-hydroxy-7-azabenzotriazole (HOAt) (231 mg, 1.70 mmol). After 10 min at room temperature the aniline hydrochloride salt was added in one portion. The mixture was left to stir at room temperature overnight, then diluted with EtOAc, washed with water, dilute aqueous HCl, water again and finally brine. The solution was then dried (MgSO_4), filtered and concentrated *in vacuo* leaving a brown foam. The product was purified by SiO_2 column chromatography using EtOAc in hexane eluent mixtures providing the desired amide (1.05 g) as a white solid.

The above amide (1.00 g, 1.87 mmol) was dispersed in 25 mL absolute EtOH. A slurry of 20% $\text{Pd}(\text{OH})_2$ in EtOH was added by pipet (230 mg). The mixture was stirred under an atmosphere of H_2 . After 3 h the reaction was filtered through diatomaceous earth and concentrated *in vacuo*, providing the debenzylated hydroxy indole amide (843 mg) as a light yellow solid.

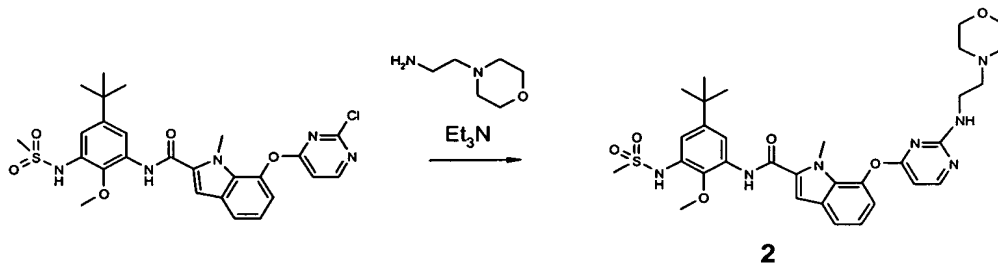
The hydroxy indole amide (824 mg, 1.85 mmol) was dissolved in 10 mL anhydrous acetonitrile. DBU (0.277 mL, 1.85 mmol) was added, followed by 2,4-dichloropyrimidine (276 mg, 1.85 mmol) and the reaction was left stirring at room

temperature for 1.5 h, then concentrated *in vacuo*. The residue was loaded on a SiO₂ column and purified, eluting with EtOAc in hexanes mixtures. The 2-chloropyrimidinyl ether (367 mg) was isolated as a white solid.

- 5 The 2-chloropyrimidinyl ether (104 mg, 0.186 mmol) was placed in 1.5 mL anhydrous THF followed by 1-methylpiperazine (0.042 mL, 0.375 mmol). The mixture was stirred in a sealed tube overnight at 75 °C. It was then allowed to cool, then water was added and the mixture was extracted with CH₂Cl₂ twice. The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*, leaving an orange foam. This
 10 was dissolved in acetonitrile and heated until product precipitated as an off-white solid that was collected by filtration through vacuum Buchner funnel and air dried. The title compound (80 mg) was obtained as an off-white solid.

15

Example 2: Synthesis of 1-methyl-7-[2-(2-morpholin-4-yl-ethylamino)-pyrimidin-4-oxyl]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

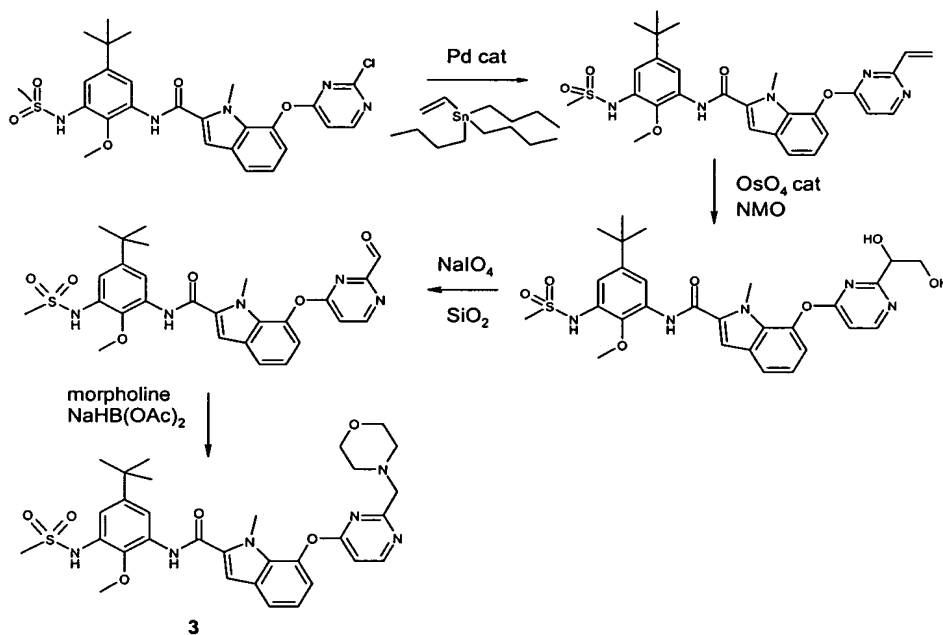


- 20 The 2-chloropyrimidinyl ether intermediate (75 mg, 0.13 mmol) (see Example 1) was dissolved in 1.0 mL anhydrous THF, treated with triethylamine (21 uL, 0.15 mmol) and 4-aminoethylmorpholine (18 uL, 0.13 mmol). The solution was placed in a sealed tube and stirred in a 75 °C bath overnight. The reaction was then allowed to cool, partitioned between water and EtOAc, and the aqueous phase was extracted with more EtOAc. The
 25 combined organic extracts were dried (MgSO₄), filtered, and concentrated *in vacuo* leaving a yellow foam (92 mg). The product was purified by SiO₂ column chromatography, using MeOH in dichloromethane eluent. The resulting white foam was suspended in a little acetonitrile and heated to boiling until it dissolved. Upon cooling

slowly cool to room temperature, crystals of the desired amino-pyriminyl ether precipitated out. These were collected by vacuum filtration with a Buchner funnel providing the title compound (57 mg), mp: 201-202 °C.

5

Example 3: Synthesis of 1-methyl-7-(2-morpholin-4-ylmethyl-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide



10

The 2-chloropyrimidinyl ether intermediate (500 mg, 0.896 mmol) (see Example 1), vinyltributyltin (600 mg, 1.89 mmol), BHT (20 mg), and (PPh₃)₄Pd (50 mg, 0.045 mmol) were suspended in degassed toluene (10 mL) under argon and heated to 115°C for 3 h. The reaction mixture was cooled, diluted with EtOAc (100 mL), washed with
 15 brine (10 mL), and dried over MgSO₄. Silica gel chromatography (gradient elution, 0% to 80% EtOAc in hexanes) provided the desired 2-vinylpyrimidinyl ether intermediate (302 mg, 61%) as a pale yellow solid.

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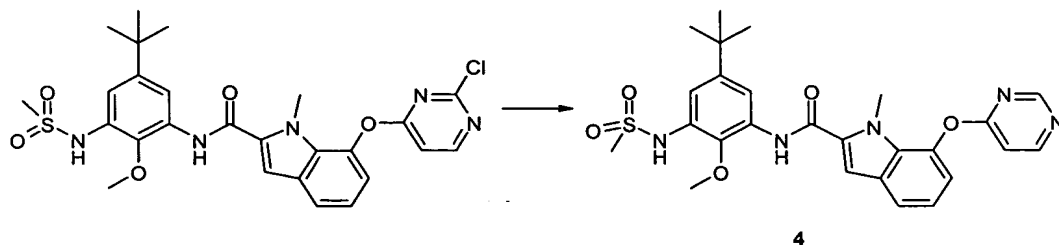
The 2-vinylpyrimidinyl ether (152 mg, 0.277 mmol) was dissolved in 8:1 acetone/water (10 mL). N-methylmorpholine-N-oxide (150 mg, 1.28 mmol) and OsO₄ (50 µL of a 2.5 wt% solution in *tert*-butanol) were added and the reaction was stirred at room

temperature for 6 h. Sodium sulfite (250 mg) in water (20 mL) was added, and the solution was stirred at room temperature for 15 min. The reaction mixture was extracted with dichloromethane (4 x 20 mL), and the combined organic extracts dried over Na₂SO₄ and concentrated. Recrystallization from dichloromethane/hexanes
 5 provided the desired diol as a white powder (105 mg, 65%).

To a vigorously stirred suspension of silica gel (20 g) in dichloromethane (80 mL) was added a solution of sodium periodate (1.40 g, 6.55 mmol) in water (10 mL) over two min. A solution of the diol (1.25 g, 2.14 mmol) in dichloromethane (10 mL) was then
 10 added in one portion. After stirring at room temperature for 2 h, the mixture was filtered through a sintered glass frit with copious dichloromethane and EtOAc washings. The filtrate was dried over MgSO₄ and concentrated to provide the desired aldehyde as a pale brown solid (1.08 g, 91%).

To a vigorously stirred solution of the aldehyde (52 mg, 0.094 mmol), morpholine (200 μL), and acetic acid (150 μL) in 1,2-dichloroethane (4 mL) was added sodium triacetoxyborohydride (100 mg, 0.472 mmol). The resulting mixture was stirred at room temperature for 16 h. Saturated NaHCO₃ (1 mL) and brine (3 mL) were added and the mixture was stirred for a further 10 min. Extraction with dichloromethane (3 x 20 mL)
 20 was followed by drying (MgSO₄), and removal of the solvent. Silica gel chromatography (gradient elution, 0 to 10% MeOH in dichloromethane, 0.3% NH₄OH) provided the title compound as an off-white solid (40 mg, 68%).

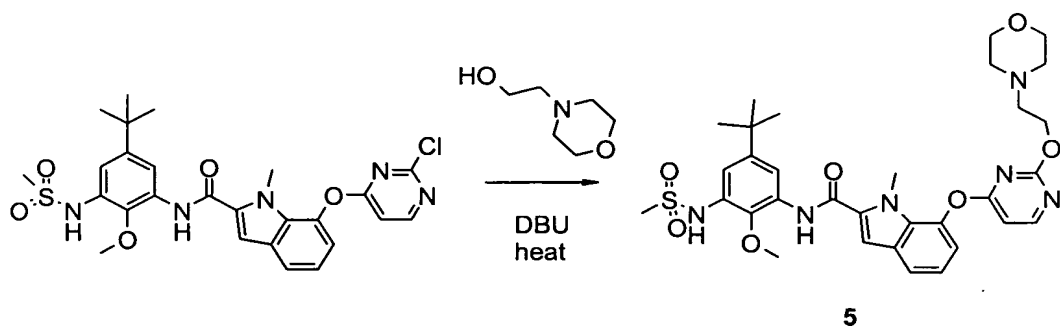
25 **Example 4: Synthesis of 1-methyl-7-(pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide**



The 2-chloropyrimidinyl ether intermediate (100 mg, 0.179 mmol) (see Example 1) was dissolved in a mixture of EtOH and CH₃CN (4:1, total 10 mL, using heat gun to complete dissolution). The reaction was cooled to room temperature under N₂ then 10% palladium-on-carbon (35 mg) was added and the reaction vessel was purged with H₂ several times. The reaction was stirred under H₂ (balloon). After stirring at room temperature for 4 h the reaction was filtered through diatomaceous earth and washed with CH₃CN. The solvents were removed *in vacuo* and the residue dissolved in CH₂Cl₂ (not totally soluble) and purified by flash column chromatography using EtOAc/hexanes as eluent mixtures, providing 24 mg of the title compound.

10

Example 5: Synthesis of 1-methyl-7-[2-(2-morpholin-4-yl-ethoxy)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide



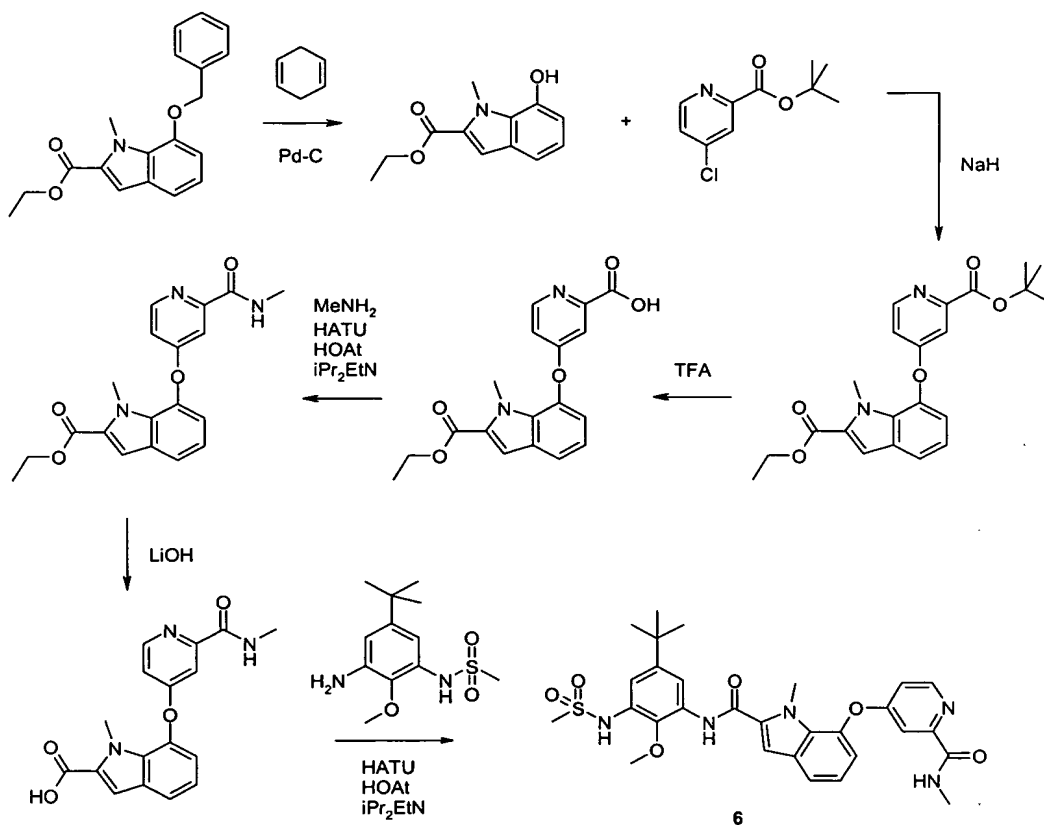
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The chloropyrimidinyl ether intermediate (see Example 1) (0.250 g, 0.448 mmol) was dissolved in 5 mL CH₃CN in a 15 mL pressure tube. In a single portion, a mixture of 4-(2-hydroxyethyl)morpholine (0.080 g, 0.61 mmol) and DBU (0.11 g, 0.73 mmol) were added. The tube was washed down with 5 mL CH₃CN, sealed, and heated to about 95 °C (oil bath temp) for 48 h. The oil bath was raised to 110 °C and heating continued another 18 h. The reaction was allowed to cool, stripped to an amber oil and partitioned between EtOAc and water. The organic phase was washed with water, then brine, and dried over MgSO₄. The organic layer was stripped again to approximately 300 mg of amber oil, absorbed onto silica, and the product purified by flash column chromatography on SiO₂ using 5-25% iPrOH in CH₂Cl₂ as eluents. Concentration of the product-rich fractions afforded 40 mg of the title compound.

25

Example 6: Synthesis of 1-methyl-7-(2-methylcarbamoyl-pyridin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

5



To a solution of the indole ester intermediate (see Example 1) (1.26 g, ~4 mmol) in 25 mL of EtOAc was added 10% Pd/C (250 mg). The reaction vessel was purged with N₂. and 1,4-cyclohexadiene (1.92 mL, 20.5 mmol) was added *via* syringe. The reaction mixture was heated to reflux for 5 h, then cooled to room temperature, filtered through a pad of diatomaceous earth, and rinsed with EtOAc. The resulting solution was evaporated to afford a pink solid which was purified by column chromatography on SiO₂ (4:1 hexanes-EtOAc) to give 740 mg of the desired 7-hydroxyindole intermediate.

15

To a solution of the 7-hydroxyindole (200 mg, 0.912 mmol) in 2 mL of dry THF was added NaH (40 mg of a 60% dispersion in mineral oil) resulting in a deep blue solution.

A solution of 4chloropyridine-2carboxylic acid *t*-butyl ester (256 mg, 1.20 mmol) in 1 mL of DMF was added and the mixture was heated to 120 °C under N₂ for 5 h. After cooling down, the reaction mixture was diluted with EtOAc, washed with water, brine, dried (Na₂SO₄) and filtered. After removal of solvents, the residue was purified by
5 column chromatography on silica gel, eluting with 4:1 hexanes-EtOAc to give 50 mg of the desired diester.

The above diester (170 mg, 0.43 mmol) was dissolved in 4 mL CH₂Cl₂, and 1,3-dimethoxybenzene and 1 mL of TFA were added and the reaction was stirred overnight.
10 After removal of the solvents, water was added to the oily residue and the pH adjusted to 3-4 with NaHCO₃ and extracted with CH₂Cl₂. The extracts were washed with brine, dried (Na₂SO₄) and filtered. After removal of the solvents, the desired carboxylic acid was used in next step without further purification.

15 To a solution of the carboxylic acid (160 mg, 0.47 mmol) in 2 mL of DMF were added Hunig's base (200 uL, 1.15 mmol), HATU (226 mg, 0.576 mmol), HOAt (8.2 mg, 0.06 mmol) and MeNH₂ (0.5 mL of a 2.0 M solution in THF, 1 mmol) successively. The reaction was stirred overnight, then diluted with EtOAc, washed with water, brine, and dried (Na₂SO₄). After removal of the solvent, the residue was purified by column
20 chromatography on SiO₂ (3:1 hexanes-EtOAc) to give 120 mg of the desired methylamide.

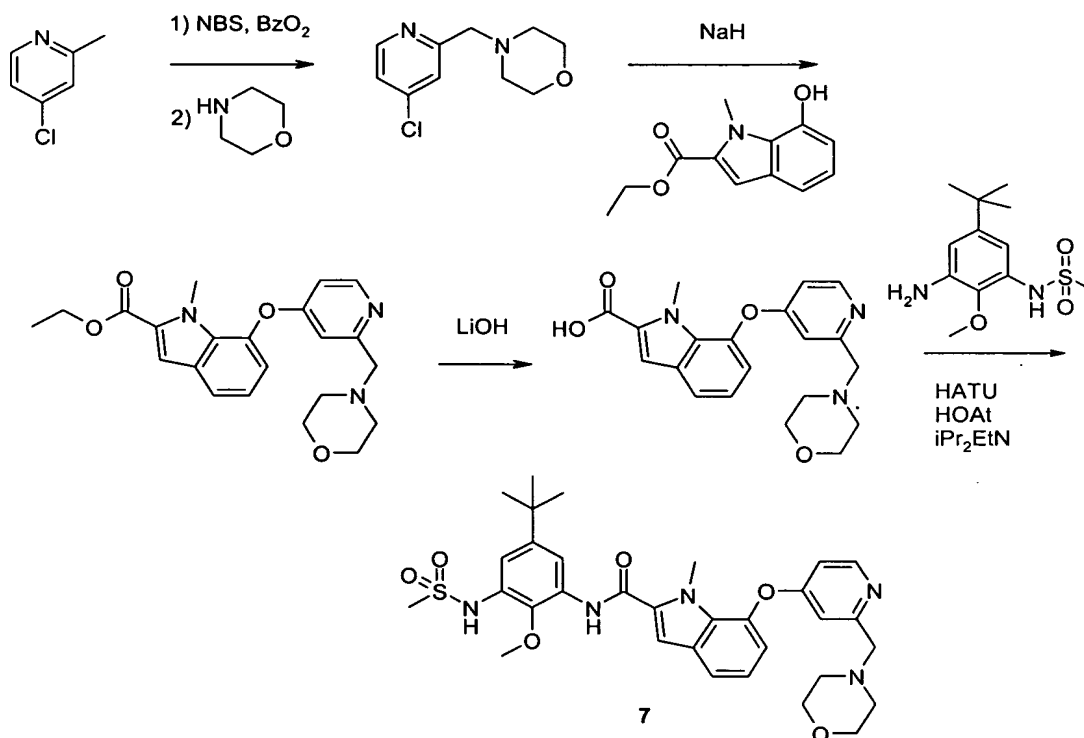
The above methylamide (110 mg, 0.311 mmol) was dissolved in 3 mL of THF and LiOH (26 mg, 0.62 mmol) was added as a solution in 1 mL water. The mixture was
25 stirred at room temperature overnight. The reaction mixture was partitioned between CH₂Cl₂ and water, and the water was separated and adjusted to pH to 3-4 with HCl and extracted again with CH₂Cl₂. The combined organic layers were washed with brine, dried (Na₂SO₄) and filtered. After removal of the solvent, the carboxylic acid was obtained as a solid which was used in next step without any purification.

30

To a suspension of the above carboxylic acid (60 mg, 0.185 mmol) in 1.5 mL of DMF was added Hunig's base (87 uL, 0.50 mmol). After 5 min, HATU (90.2 mg, 0.23 mmol) and HOAt (5.0 mg, 0.037 mmol) were added followed by N-(3-amino-5-tert-

butyl-2-methoxy-phenyl)-methanesulfonamide (51.8 mg, 0.190 mmol). The mixture was stirred overnight and was then diluted with EtOAc, washed with water, brine, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified twice by flash column chromatography (3-5% MeOH in CH_2Cl_2) to give 85 mg of the desired product with some impurities. Final purification by reverse-phase HPLC (water:acetonitrile) gave 45 mg of the title compound.

Example 7: Synthesis of 1-methyl-7-(2-morpholin-4-ylmethyl-pyridin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide



A mixture of the 2-methyl-4-chloropyridine (1.00 g, 7.84 mmol), NBS (1.42 g, 8.00 mmol) and benzoyl peroxide (~10 mg) in 10 mL of CCl_4 was heated at reflux for 5 h. After cooling down, the reaction mixture was filtered and filtrate was concentrated to give the crude products mixture, which was dissolved in DMF and treated with morpholine (1.00 mL) and K_2CO_3 (1 g). The mixture was stirred overnight. The mixture was then diluted with EtOAc, washed with water, brine, dried over Na_2SO_4 , filtered and

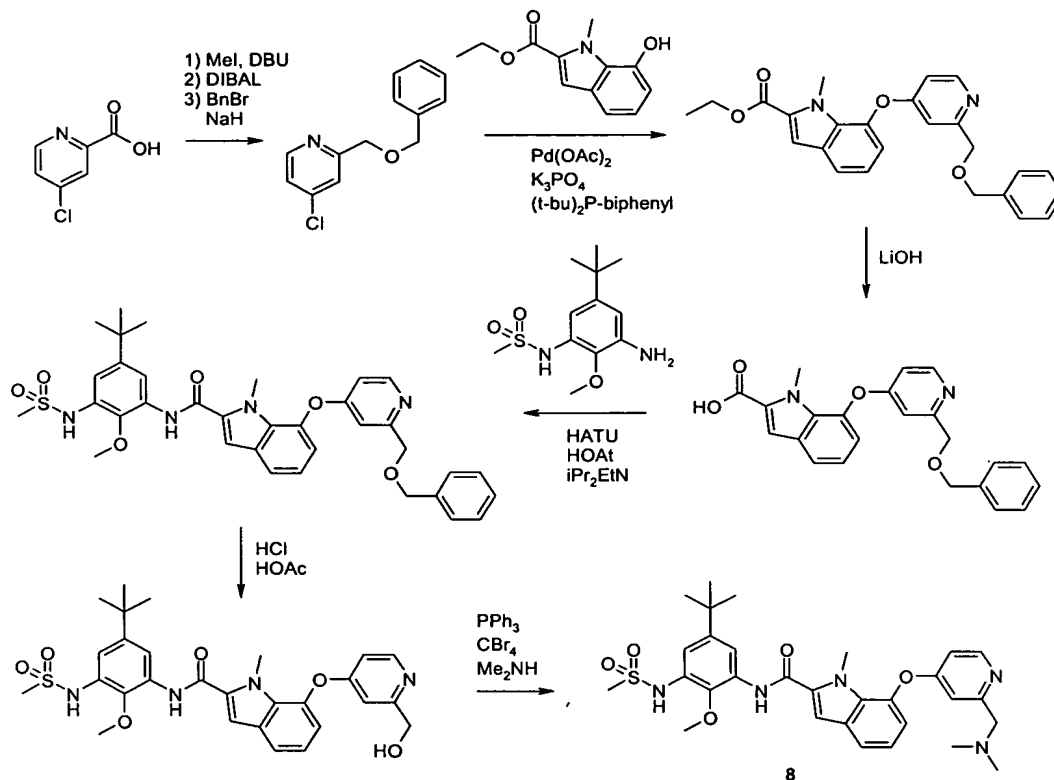
concentrated *in vacuo*. The crude product was purified by column chromatography on SiO₂ to give 400 mg of the desired 2-morpholinomethyl-4-chloropyridine.

To a solution of the 7-hydroxyindole ester (see Example 6) (473.6 mg, 2.16 mmol) in 10 mL of dry DMF was added NaH (86.4 mg of a 60% dispersion in mineral oil, 2.16 mmol), resulting in a deep blue solution. A solution of the 4-chloropyridine intermediate from above (380 mg, 1.79 mmol) in 3 mL of DMF was added and the mixture was heated to 140 °C in a sealed tube for 4.5 h. After cooling down, the reaction mixture was diluted with EtOAc, washed with water, brine, dried (Na₂SO₄) and filtered. After removal of solvent, the residue was purified by column chromatography on silica gel eluting with 1-4% MeOH in CH₂Cl₂ to give 240 mg of a mixture of unreacted chloropyridine and the desired ether intermediate, which was used in next step without further purification.

The mixture of the above ether and unreacted chloropyridine was dissolved in 3 mL of THF and was treated with 1 mL of aqueous LiOH (60 mg) solution. The reaction mixture was stirred overnight and then was concentrated *in vacuo*. The residue was diluted with 1 M NaOH and extracted with ether to remove unreacted 7-hydroxyindole ester and chloropyridine. The aqueous layer was then acidified with 2 M HCl to pH 4-5 and extracted with CH₂Cl₂ 6 times. The combined organic extracts were dried (Na₂SO₄), filtered and concentrated to give 68 mg of the desired indole acid.

To a solution of the indole acid (65.0 mg, 0.177 mmol) in 2 mL of DMF was added Hunig's base (87 uL, 0.50 mmol). After 5 min, HATU (90.2 mg, 0.23 mmol) and HOAt (5 mg, 0.037 mmol) were added, and then N-(3-amino-5-tert-butyl-2-methoxy-phenyl)-methanesulfonamide (49 mg, 0.180 mmol). The mixture was stirred overnight. The reaction mixture was diluted with EtOAc, washed with water, brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude product was purified by preparative TLC (10% MeOH in DCM) to give 35 mg of product, which was purified by reverse-phase HPLC to give 20 mg of the title compound.

Example 8: Synthesis of 7-(2-dimethylaminomethyl-pyridin-4-yloxy)-1-methyl-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide



- 5 A mixture of 4-chloropyridine-2-carboxylic acid (2.00 g, 12.69 mmol), methyl iodide (1.25 mL, 20.0 mmol) and DBU (3.34 mL, 22.0 mmol) in 20 mL of dry acetonitrile was stirred over 2 days. The reaction mixture was diluted with ether, washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel to give 1.6 g of the desired methyl ester.

10

- To a solution of DIBAL in toluene (1 M, 12.3 mL, 12.3 mmol) and THF (1:1) in an ice-salt bath, was added a solution of the above ester (700 mg, 4.10 mmol) in 10 mL of THF. After addition, the reaction mixture was allowed to warm up to room temperature and stir for 3h. The mixture was then poured into crushed ice with 5 mL of 4M NaOH, extracted with EtOAc, dried over Na_2SO_4 and concentrated *in vacuo* to give 450 mg of the desired alcohol, which was used in next step without purification.
- 15

To a solution of the above alcohol (430 mg, 3.0 mmol) in DMF (10 mL) was added NaH (144 mg of a 60% dispersion in mineral oil, 3.60 mmol) and the mixture was then cooled in an ice bath. Benzyl bromide (437 μ L, 3.60 mmol) was then added and the mixture was stirred at room temperature for 3 h. After normal aqueous work-up and short column chromatographic purification, 600 mg of desired benzyl ether was obtained.

A Schlenk tube was charged with Pd(OAc)₂ (16 mg, 0.07 mmol), K₃PO₄ (525 mg, 2.40 mmol), di-*t*-butylbiphenylphosphine (42 mg, 0.14 mmol) and the 7-hydroxyindole ester (see Example 6) (307 mg, 1.4 mmol), and capped with a septum and purged with argon. A solution of the benzyl ether from above (270 mg, 1.16 mmol) in 3 mL of toluene was then added via syringe. The mixture was heated at 100 °C with stirring under argon for 6 h. The reaction mixture was filtered through a layer of diatomaceous earth and the solid residue was rinsed with CH₂Cl₂. The combined filtrate was concentrated. The crude product was purified by column chromatography to give 61% yield of the desired indole ether.

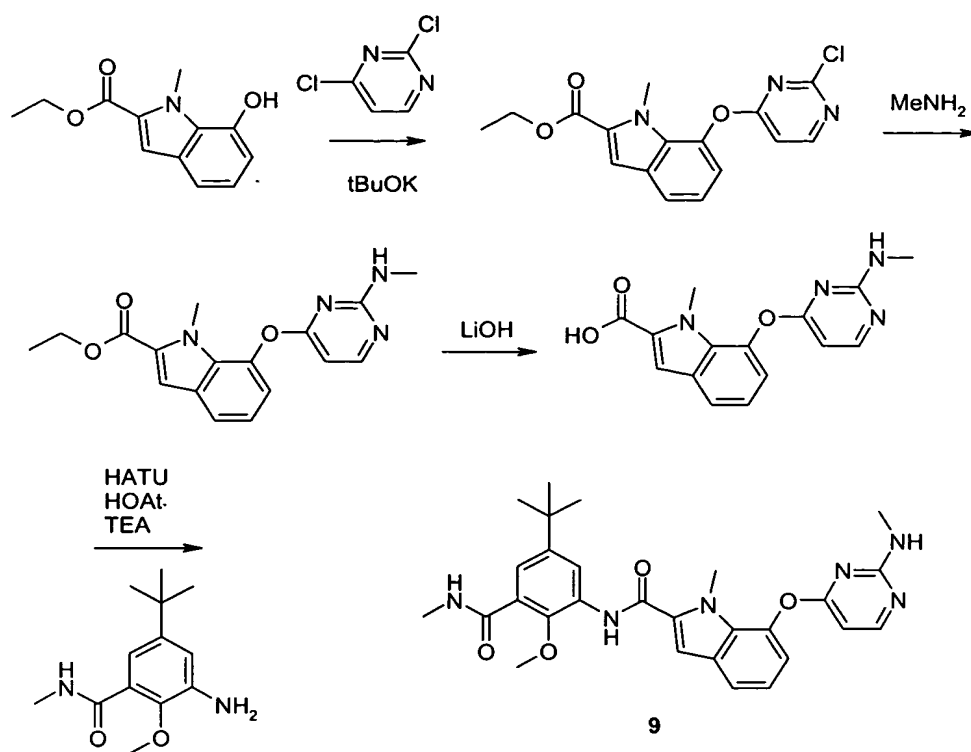
To a solution of the indole ether (400 mg, 0.96 mmol) in 8 mL THF was added a solution of LiOH (120 mg, 2.86 mmol) in 2.5 mL of H₂O. The mixture was stirred overnight, then was diluted with water, acidified with 2 N HCl to pH 4-5, and extracted with CH₂Cl₂. The combined extracts were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo* to give 360 mg of desired carboxylic acid, which was pure enough for the next step without purification.

To a solution of the indole carboxylic acid (360 mg, 0.93 mmol) in 4 mL of DMF was added Hunig's base (418 μ L, 2.4 mmol). After 5 min, HATU (439 mg, 1.12 mmol) and HOAt (12 mg, 0.09 mmol) were added and then N-(3-amino-5-tert-butyl-2-methoxyphenyl)-methanesulfonamide (253 mg, 0.93 mmol). The mixture was stirred overnight. The reaction mixture was diluted with EtOAc, washed with water, brine, dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by column chromatography (1:2 hexanes-EtOAc) to give 390 mg of the desired amide.

To a solution of the amide (390 mg, 0.61 mmol) in 4 mL of HOAc was added 2 mL of concentrated HCl and the mixture was heated at 100 °C for 3 h. After cooling down, the reaction mixture was poured into crushed ice, adjusted to pH to 5-6, extracted with EtOAc, washed with saturated aqueous NaHCO₃, brine, and dried over Na₂SO₄. After
5 removal of the solvent, the residue was purified by column chromatography (3-5% MeOH in CH₂Cl₂) to give 180 mg of the desired debenzylated pyridine-methanol.

To a solution of the pyridine-methanol (63 mg, 0.11 mmol) and CBr₄ (76 mg, 0.23 mmol) in 2 mL of CH₂Cl₂ was added Ph₃P (36 mg, 0.14 mmol) at 0 °C and the mixture
10 was stirred at 0 °C for 1 h. The reaction mixture was concentrated *in vacuo* and the resulting yellow foam was dissolved in 2 mL DMF, to which was added 1 mL of 2 M Me₂NH in THF and solid K₂CO₃. The mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc, washed with water, brine, dried (Na₂SO₄) and concentrated *in vacuo*. The crude product was purified by column chromatography
15 to give 15 mg of the title compound.

Example 9: Synthesis of 1-methyl-7-(2-methylamino-pyrimidin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-2-methoxy-3-methylcarbamoyl-phenyl)-amide



To a solution of 7-hydroxyindole ester (see Example 6) (2.10 g, 10 mmol) in DMSO (25 mL) was added t-BuOK solution in THF (1.0 M, 10 mL, 10 mmol) at room temperature. The reaction color changed from red to green. 2,4-Dichloropyrimidine (1.50 g, 10 mmol) was then added. The reaction mixture was heated to 70 °C for 3 h. The reaction was cooled, diluted with H₂O and extracted with EtOAc. The combined organics were washed with water and brine, dried over MgSO₄, filtered and concentrated to give a crude solid. The solid was triturated with 30%EtOAc/hexanes and filtered to give 1.4 g of the desired ether. The filtrate was concentrated down and purified by column chromatography on SiO₂ (15%-40% EtOAc/hexanes eluent) to give an additional 1.2 g of the ether intermediate as a white solid, for a combined yield of 2.6 g (78%).

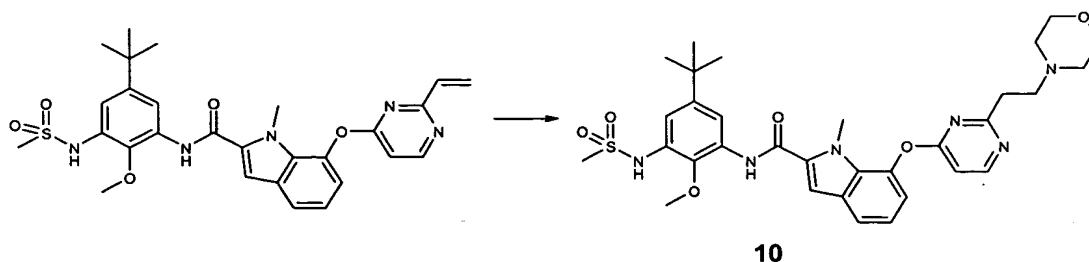
To a solution of the above chloro-pyrimidinyl ether (1.00 g, 3.01 mmol) in 15 mL anhydrous THF in a sealed tube was added 6.0 eq of MeNH₂ solution in THF. The reaction was heated at 70 °C overnight. It was then cooled down to room temperature, diluted with water and extracted with EtOAc. The organics were washed with brine, dried, filtered and concentrated to give a foam, which was purified by flash column

chromatography on SiO₂ (20%-50% EtOAc/hexanes eluent) to give 812 mg of desired methylamino-pyrimidine intermediate.

To a solution of the above intermediate (812 mg, 2.49 mmol) in MeOH/THF (15mL/15mL) was added LiOH as an aqueous solution (313 mg in 2 mL of H₂O). The reaction color changed to light green. The reaction was stirred at room temperature for 6 h, then concentrated *in vacuo*. Water was added, the mixture was washed with Et₂O and the organic layer was discarded. The aqueous phase was acidified to pH 3-4 with 3N HCl and extracted with EtOAc. The combined organic extracts were dried, filtered (MgSO₄) and concentrated down to give 580 mg of the indole carboxylic acid as a pale pink solid.

To a solution of the above indole carboxylic acid (122 mg, 0.41 mmol) in DMF were added HATU (141 mg, 0.37 mmol), TEA (104 uL, 0.74 mmol) and HOAt (25 mg, 0.19 mmol). After 10 min, the aniline intermediate (88 mg, 0.37 mmol) was added in one portion. The mixture was stirred at room temperature for 8 h. The reaction was then diluted with EtOAc and washed with water. Most starting aniline was removed by washing with 0.5 N aqueous HCl. The resulting organics were dried (MgSO₄), filtered and concentrated to give an oil which was purified by column chromatography on SiO₂ (3%-10% MeOH/CH₂Cl₂ eluents) followed by preparative TLC to give 110 mg of the title compound.

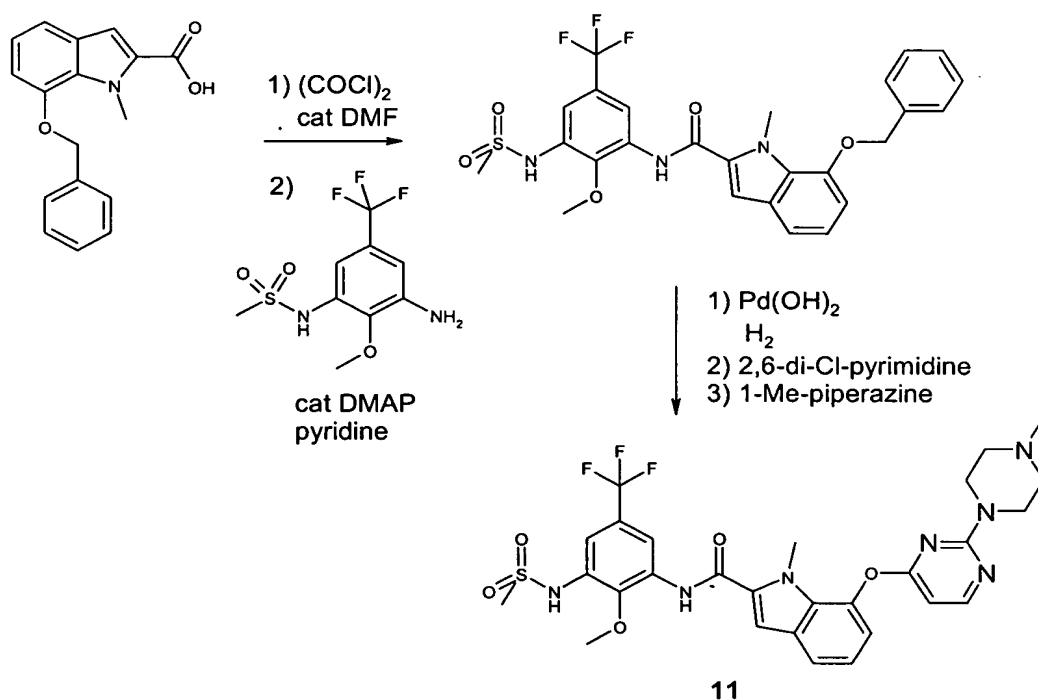
Example 10: Synthesis of 1-methyl-7-[2-(2-morpholin-4-yl-ethyl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (5-tert-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide



To a suspension in EtOH (3 mL) of the olefin illustrated above (200 mg, 0.364 mmol) was added morpholine (65 μ L, 0.75 mmol) and acetic acid (35 μ L, 0.61 mmol). The mixture was heated to 80 $^{\circ}$ C under nitrogen for 4 h, after which time a homogeneous solution was obtained. The reaction was diluted with dichloromethane (10 mL) and stirred over anhydrous K_2CO_3 for 30 min. The solution was then filtered and concentrated. Trituration of the residue with Et₂O provided the product (221 mg, 95%) as a tan powder.

10

Example 11: Synthesis of 1-methyl-7-[2-(4-methyl-piperazin-1-yl)-pyrimidin-4-yloxy]-1H-indole-2-carboxylic acid (3-methanesulfonylamino-2-methoxy-5-trifluoromethyl-phenyl)-amide



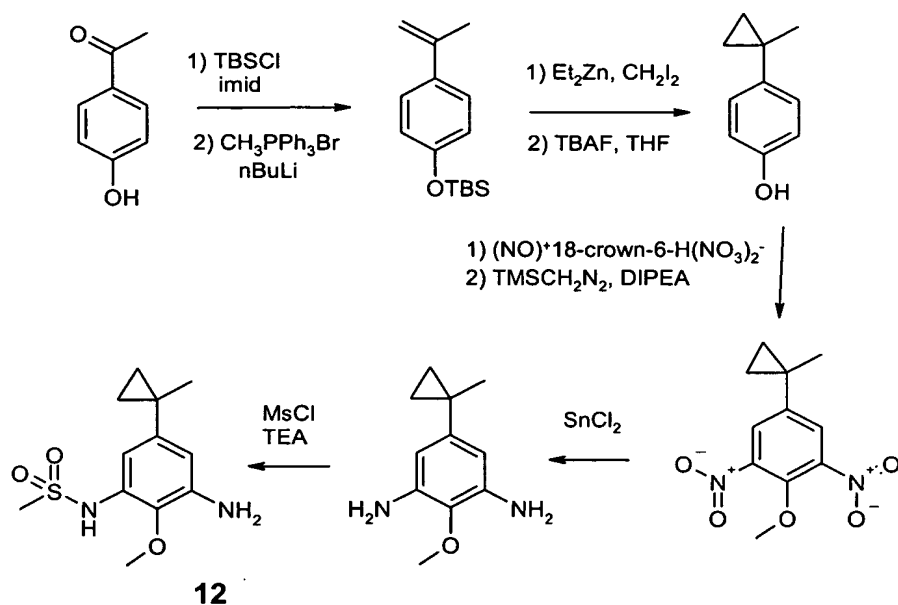
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To a suspension of the indole carboxylic acid (2.10 g, 7.47 mmol) in dichloromethane (40 mL) was added oxalyl chloride (6.0 mL of a 2.0 M solution in dichloromethane, 12 mmol) and DMF (10 μ L) under an atmosphere of dry N_2 . After stirring at ambient

temperature for 1.5 h, the resulting yellow solution was concentrated *in vacuo* to provide the crude acid chloride as a yellow powder. This material was dissolved in THF (50 mL), and to this solution was added N-(3-amino-5-tert-butyl-2-methoxy-phenyl)-methanesulfonamide (2.13 g, 7.50 mmol), pyridine (971 μ L, 12.0 mmol) and DMAP (50 mg). The reaction was stirred at ambient temperature for 4 days, then taken up in dichloromethane (300 mL), washed with saturated NaHCO₃ (40 mL), and concentrated *in vacuo*. The resulting solids were triturated with ether to provide the product (2.94 g, 72%) as an analytically pure white powder.

O-de-benzoylation and further transformation to the title compound were performed as previously described (Example 1) to afford the title compound.

Example 12: Synthesis of N-[3-amino-2-methoxy-5-(1-methylcyclopropyl)-phenyl]-methanesulfonamide



To a solution of 4-hydroxyacetophenone (10.0 g, 73.5 mmol) in DMF (74 mL) was added imidazole (12.0 g, 176.3 mmol) and *tert*-butyldimethylsilyl chloride (13.3 g, 88.1 mmol). The colorless solution was stirred for 0.75 h at room temperature then quenched with saturated aqueous NaHCO₃. The aqueous phase was extracted with hexanes and the combined organic layers were washed with saturated aqueous NaHCO₃. The organic

layers were dried over sodium sulfate, filtered, and concentrated to provide the silyl ether (18.0 g, 98%) as a white solid which was utilized without further purification.

5 Methyl(triphenylphosphonium) bromide (17.1 g, 48.0 mmol) was suspended in THF (96 mL) and cooled to 0 °C. *n*-Butyllithium (2.5 M in hexane, 19.2 mL, 48.0 mmol) was added dropwise to the mixture. The red solution was stirred at room temperature for 0.5 h. The acetophenone silyl ether (10.0 g, 40.0 mmol) from above was added. The solution turned bright yellow and a white precipitate formed. The mixture was stirred for 1 h at room temperature and then the solution was quenched with saturated aqueous
10 NaHCO₃. The aqueous phase was extracted with diethyl ether and the combined organic layers were washed with saturated aqueous NaHCO₃. The organic layers were dried over sodium sulfate, filtered and concentrated. The resulting mixture was eluted through a plug of silica gel (hexanes) and the filtrate was concentrated to provide the styrene (8.36 g, 84%) as a colorless oil.

15

Diethylzinc (1.0 M in hexanes, 69 mL, 69 mmol) was added to a solution of the above styrene intermediate (6.85 g, 27.6 mmol) in dichloroethane at 0 °C. Diiodomethane (11.2 mL, 138 mmol) was then added dropwise to the solution and the resulting mixture was stirred at 0 °C for 0.5 h and allowed to warm to room temperature for 2 h. The
20 opaque mixture was quenched with saturated aqueous NH₄Cl. The aqueous phase was extracted with methylene chloride and the combined organic layers were washed with saturated aqueous NaHCO₃. The organic layers were dried over sodium sulfate, filtered through diatomaceous earth, and concentrated. The crude residue was dissolved in THF (50 mL) and TBAF (1.0 M in THF, 28 mL, 28 mmol) was added at room temperature.
25 The solution was stirred for 2 h and then quenched with aqueous 1.0 M HCl. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with saturated aqueous NaHCO₃. The organic layers were dried over sodium sulfate, filtered and concentrated. Purification by silica-gel chromatography (1% 2-propanol/12% EtOAc in hexanes) provided the phenol (2.77 g, 68%) as a white solid:

30

(NO)₁₈-crown-6•H(NO₃)₂¹ (18.0 g, 43.0 mmol) was added to a solution of phenol (2.77 g, 18.7 mmol) in EtOAc. The reaction mixture was heated to reflux for 5 min and then cooled to room temperature. The mixture was poured onto aqueous 1.0 M HCl.

The aqueous phase was extracted with diethyl ether. The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was dissolved in acetonitrile/MeOH (9:1, 62 mL), cooled to 0 °C and *N,N*-diisopropylethylamine (13 mL, 74.8 mmol) was added slowly. The deep red solution was warmed to room temperature and trimethylsilyldiazomethane (2.0 M in hexane, 18.7 mL, 37.4 mmol) was added slowly to control nitrogen evolution. After stirring at room temperature for 0.5 h, the mixture was concentrated and partitioned between methylene chloride and saturated aqueous NH₄Cl. The aqueous layer was extracted with methylene chloride and the combined extracts were dried over sodium sulfate, filtered and concentrated. Purification by silica-gel chromatography (6% EtOAc in hexanes) provided the dinitroanisole (2.21 g, 47%) as a red oil.

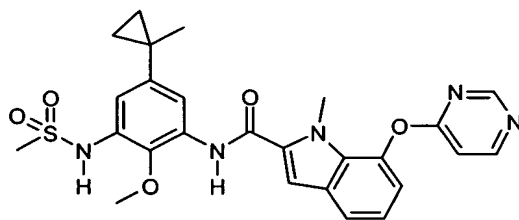
Tin(II)chloride dihydrate (11.9 g, 52.6 mmol) was added to a solution of the above dinitroanisole (2.21 g, 8.76 mmol) in EtOAc (30 mL). The mixture was heated to reflux for 0.25 h upon which the solution became red in color. The solution was cooled to room temperature and poured onto aqueous 2.0 M NaOH. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with saturated aqueous NaHCO₃. The organic layers were dried over sodium sulfate, eluted through a plug of silica gel (1% ammonium hydroxide in methylene chloride), and the filtrate was concentrated. The residue was dissolved in diethyl ether and extracted (3x) with 1.0 M HCl. The pH of the combined aqueous layers was adjusted to pH=12 with 2.0M NaOH and extracted with methylene chloride. The combined organic layers were dried over sodium sulfate, filtered and concentrated to provide diaminoanisole (860 mg, 52%) as a red oil.

Triethylamine (521 µL, 3.74 mmol) was added to a solution of the above diaminoanisole (718 mg, 3.74 mmol) in methylene chloride at -10 °C. Methanesulfonyl chloride (290 µL, 3.74 mmol) was then added dropwise over a 10 min period and the resulting solution was allowed to slowly warm to room temperature over 2 h. The mixture was quenched with saturated aqueous NaHCO₃ and the aqueous layer was extracted with methylene chloride. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (1% ammonium hydroxide/35% EtOAc in hexanes to 1% ammonium hydroxide/50%

EtOAc in hexanes) provided a red solid which was triturated with a diethyl ether/hexanes (1:1) to yield the title compound (510 mg, 51%) as a pale brown solid, mp 144–146 °C.

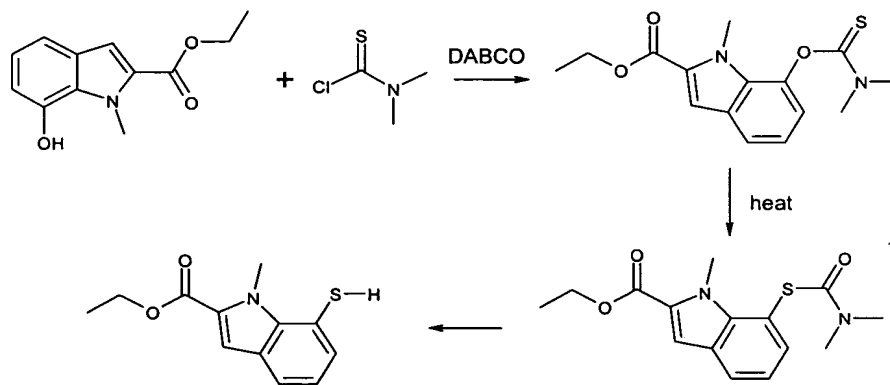
- 5 This intermediate can then be coupled to the indole core and reacted further by the procedures described in the examples above, to form desired analogous indole amides.

For example, the product of Example 12 was used to prepare the following compound:



10

Example 13: Synthesis of 7-mercapto-1-methyl-1H-indole-2-carboxylic acid ethyl ester



15

13

- 7-Hydroxy-1-methylindole-2-carboxylic acid ethyl ester (1.06 g; 0.005 mol) was dissolved in 8 mL DMF in a 3-neck round bottom flask under nitrogen purge. Diazabicyclo[2.2.2.]octane (DABCO) (1.12 g, 0.010 mol) and Me₂NC(=S)Cl (1.236 g, 0.010 mol) were added sequentially, each in a single portion,. The mixture was left stirring at room temperature overnight. A suspension formed. The reaction mixture was
- 20

poured onto water and extracted 3X with EtOAc. The combined organic layers were washed 3X with water, then brine, then dried over MgSO_4 , concentrated to a semi-solid, ca 1.6 g.

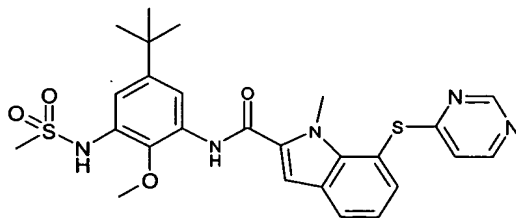
5 The above residue was taken up in hot i-PrOH (about 30 mL) and treated with charcoal. The solution was cooled overnight in a freezer, then the resulting beige solid was filtered off and washed with cold i-PrOH, then petroleum ether providing the desired thiocarbamate (0.92 g).

10 The above thiocarbamate (31 mg; 0.0001 mol) was added into a pressure tube, along with Me_2NPh (0.63 mL; 0.005 mol) and a magnetic stir bar. The tube was heated in a microwave oven to 250 °C for 10 min. The reaction mixture was then poured onto 4 N aqueous HCl and the gummy precipitate was extracted with EtOAc. The solution was allowed to evaporate providing the desired isomerized intermediate.

15

The resulting intermediate can be hydrolyzed to form the desired thiol, which can then be further reacted by the methods described above for the analogous 7-hydroxyindole intermediate to form the desired thioether derivatives.

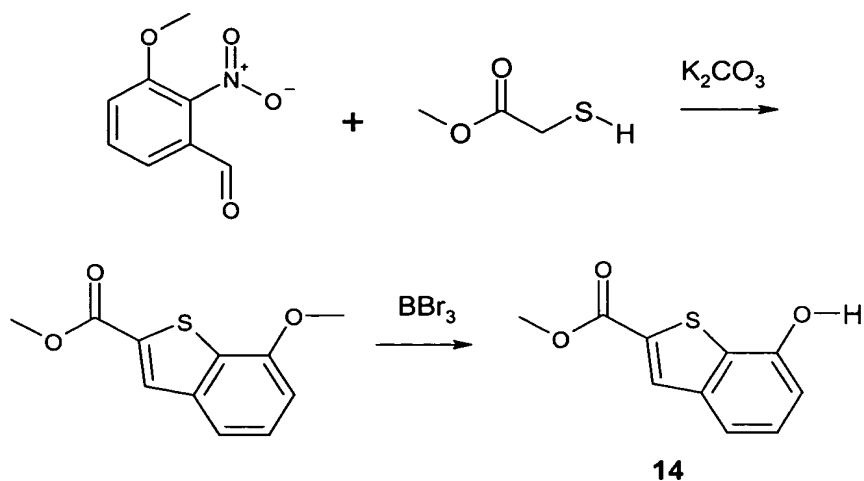
20 For example, the following compound may be prepared from the above thiol using the methods described in the above examples:



25

Example 14: Synthesis of 7-hydroxy-benzo[b]thiophene-2-carboxylic acid methyl ester

30



To a 150 mL heating flask was added 1 g (5.52 mmol) of 3-methoxy-2-nitro-
 5 benzaldehyde, 0.5 mL (5.7 mmol) of mercapto-acetic acid methyl ester, 1.8 g (13 mmol)
 of potassium carbonate and 50 mL of anhydrous DMF. The opaque, gold solution was
 stirred overnight at 60 °C in a sealed tube. After 14 h the reaction was poured into 200
 mL of water, stirred 2 h, and extracted with EtOAc to provide 1 g (81%) of the desired
 intermediate, which was used without further purification.

10

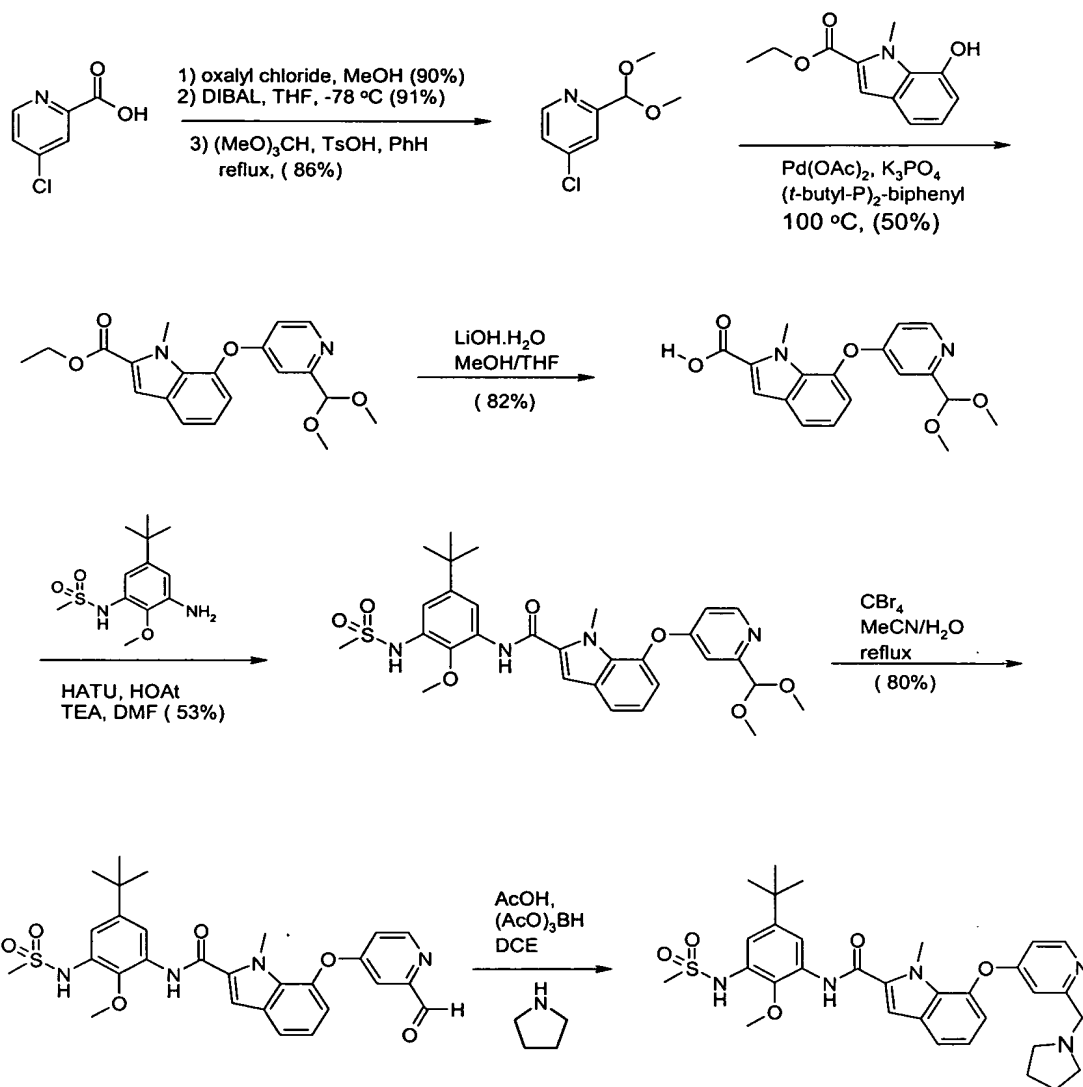
Dissolved 1 g (4.5 mmol) of the above intermediate in about 50 mL CH₂Cl₂ in a 500
 mL 3-neck round-bottom flask under nitrogen purge and cooled in an ice/acetone bath.
 Placed the BBr₃/CH₂Cl₂ solution (3 eq) in addition funnel, and added dropwise at such a
 15 rate that the temperature was maintained < 5 °C throughout. Allowed to warm to room
 temperature and continued stirring overnight. The reaction was cooled back down in an
 ice/acetone bath and added 50 mL MeOH dropwise; initially very slowly, since it was
 exothermic. After the addition of MeOH was complete, the reaction was allowed to
 warm to room temperature and then concentrated *in vacuo* to obtain the title compound
 20 (900 mg, 93%).

25

The 7-hydroxybenzothiophene intermediate can then be reacted further as described in
 Examples above for 7-hydroxyindole to produce compounds of formula I

Example 15: Synthesis of 1-methyl-7-(2-pyrrolidin-1-ylmethyl-pyridin-4-yloxy)-1H-indole-2-carboxylic acid (5-*tert*-butyl-3-methanesulfonylamino-2-methoxy-phenyl)-amide

5



To a suspension of 4-chloropyridine-2-carboxylic acid (4.5 g, 29.0 mmol) in methylene chloride (120 mL) was added oxalyl chloride (3.0 mL, 1.2 eq) under Ar₂. The reaction was cooled to 0 °C, added 500 uL of DMF. A large amount of gas was generated *in situ*. The reaction was stirred at room temperature for 1.5 h then concentrated. Dry MeOH (50 mL) was added to the crude acyl chloride residue. The reaction was stirred at room

temperature for 0.5 h then quenched with NaHCO_3 (5%) to neutral, extracted with EtOAc, and washed with brine. The combined organics were dried over MgSO_4 , filtered and concentrated *in vacuo* to give 5.0 g of crude solid which was triturated with 5%EtOAc/hexane to give the desired intermediate methyl ester as a light yellow solid (4.5 g, 90%).

To a solution of the above methyl ester (2.5 g, 14.6 mmol) in 100 mL of dry THF at -78°C was added diisobutylaluminum hydride dropwise (1.0 M in THF, 29.1 mmol) and the reaction mixture was stirred at that temperature under Ar_2 for 2 h. The reaction was quenched with MeOH at -78°C and then sodium potassium tartrate solution (~ 1.0 M, 180 mL) was added and the mixture was stirred and warmed up to room temperature over 1 h. The slurry was diluted with EtOAc (60mL) and the organic layer was separated and washed with brine and dried with sodium sulfate. The solvent was removed under mild vacuum at room temperature (volatile compound) to give the desired aldehyde (1.87 g, 91%) which solidified as a light yellow crystal by standing at room temperature.

To a solution of the above aldehyde (1.6 g, 11.3 mmol) in 50 mL of MeOH (dry) was added $\text{TsOH}\cdot\text{H}_2\text{O}$ (363 mg, 0.17 eq) and $(\text{MeO})_3\text{CH}$ (5mL). The reaction was heated up to reflux for 2 h then partitioned between EtOAc and water. The organic phase was then washed with NaHCO_3 solution and brine. The combined organics were dried over MgSO_4 , filtered and concentrated *in vacuo* to give the desired 4-chloro-2-dimethoxymethyl-pyridine as a light yellow oil (1.83 g, 86%).

A sealed tube was charged with $\text{Pd}(\text{OAc})_2$ (57.47 mg, 0.06eq), K_3PO_4 (1.904g, 2.0 eq), di-*tert* butyl phosphine biphenyl (152.7 mg, 0.12 eq) and 7-hydroxy-methylindole-2-carboxylic acid methyl ester (934.8 mg, 4.26 mmol) and toluene (20 mL), and capped with a septum. The system was degased and charged with argon, repeated for a couple of times. Then a solution of the 4-chloro-2-dimethoxymethyl-pyridine (800 mg, 4.26 mmol) from above in 4 mL of toluene was added via syringe. The mixture was heated at 100°C with stirring under argon for 3 h. The reaction was cooled to room temperature, and the reaction mixture was filtered through a pad of diatomaceous earth and rinsed with methylene chloride. The combined filtrates were concentrated *in vacuo*. The crude

products were purified by silica gel chromatography (30%--70%EtOAc/hex) to give the desired ether (790 mg, 50%) as a brown oil.

To a solution of the above ether (770 mg, 2.1 mmol) in THF/MeOH (25 mL/10 mL) was added LiOH.H₂O (218.1 mg, 2.50 eq) dissolved in 3 mL of water. The clear reaction solution was stirred at room temperature for 5 h, then concentrated *in vacuo*. The residual aqueous solution was diluted with water (15 mL), and extracted with ether. The organic layer was discarded. The aqueous layer was acidified to pH 5 with 1.4 N HCl (~2.5 mL). A large amount of white precipitates were extracted with 200 mL of EtOAc and washed with brine. The combined organics were dried over MgSO₄, filtered and concentrated *in vacuo* to give the desired indole-2-carboxylic acid intermediate (644 mg, 90.5%) as a white foam.

To a solution of the above carboxylic acid (651 mg, 1.9 mmol) in DMF (20 mL) were added HATU (723.2 mg, 1.0 eq) diisopropylethylamine (662.6 uL, 2.0 eq) and HOAt (129.4 mg, 0.5 eq). After 10 min, N-(3-amino-5-tert-butyl-2-methoxy-phenyl)-methanesulfonamide was added in one portion. After stirring at room temperature overnight, the reaction was worked up with EtOAc, washed with water and brine. The combined organics were dried over MgSO₄, filtered and concentrated *in vacuo* to give an oil which was purified by silica gel Chromatography (50%EtOAc/hexanes) to give the desired amide (1.03 g, 91%) as a white foam.

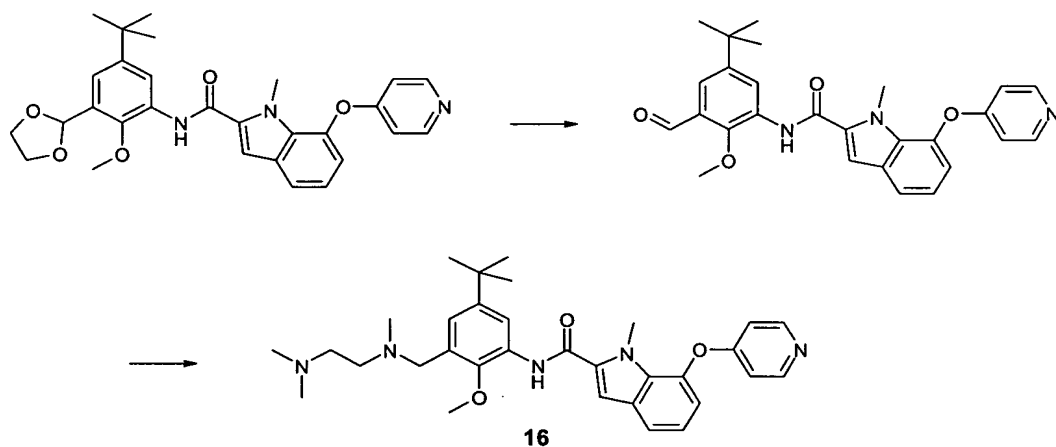
To a solution of the above amide (1.08 g, 1.81 mmol) in acetonitrile and water (20 mL/20 mL) was added CBr₄ (905 mg, 2.0 eq). The reaction was refluxed (oil bath temperature: 80 °C) overnight. The reaction was cooled to room temperature, adjusted to pH 7 with NaHCO₃ solution, extracted with EtOAc until no desired product was left in the aqueous layer. The combined organics were dried over MgSO₄, filtered and concentrated to give 1.5 g (>100%) of a light brown colored foam which was purified by silica gel chromatography (20%--70%EtOAc/hexanes) to provide the desired aldehyde intermediate as a yellow foam.

To a solution of the above aldehyde (80 mg, 0.145 mmol) in dichloroethane (10 mL) were added glacial HOAc (273 uL) and pyrrolidine (375 uL). The reaction was stirred

at room temperature for 20 min. The reaction solution became cloudy.

Triacetoxyborohydride (245 mg) was added to the reaction mixture. The reaction was stirred at room temperature for 1 h, then NaHCO_3 (saturated solution) was added, the mixture stirred for 10 min, then extracted with methylene chloride. The combined organics were washed with brine, dried over MgSO_4 , filtered and concentrated down to give 85 mg of foam which was >97% pure by HPLC and ^1H NMR. The foam was further purified by silica gel chromatography (5%--8% MeOH/methylene chloride) to provide the title compound (75 mg, 85%).

Example 16: Synthesis of 1-methyl-7-(pyridin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-[(2-dimethylamino-ethyl)-methyl-amino]-methyl)-2-methoxy-phenyl)-amide



To a solution of 1-methyl-7-(pyridin-4-yloxy)-1H-indole-2-carboxylic acid (5-tert-butyl-3-[1,3]dioxolan-2-yl-2-methoxy-phenyl)-amide (0.20 g, 0.40 mmol) in THF (3.00 mL) was added 2.0 N HCl (2 mL). The solution was allowed to stir at room temperature and under an ambient atmosphere for 17.5 h. The solution was diluted in EtOAc (20 mL) and transferred to a separatory funnel. The aqueous layer was separated and the organic layer was washed with saturated NaHCO_3 solution (2 x 10 mL), water (1 x 10 mL), brine (1 x 10 mL), dried over MgSO_4 , filtered and the solvent was evaporated to give the desired aldehyde as a yellow foam (0.16 g, 90%).

To a solution of the above aldehyde (0.04 g, 0.09 mmol) in dichloroethane (2.00 mL) was added acetic acid (0.06 mL, 1.06 mmol) followed by the dropwise addition of *N,N,N'*-trimethylethylenediamine (0.28 mL, 2.18 mmol) at 0 °C. The solution was
5 allowed to warm to room temperature and was stirred for 30 min., followed by the batchwise addition of sodium triacetoxyborohydride (0.05 g, 0.22 mmol). The reaction was allowed to stir for 17.5 h under an ambient atmosphere and at room temperature. The solution was diluted with EtOAc (10 mL) and quenched with 3% NH₄OH (1 mL). The biphasic system was transferred to a separatory funnel and the aqueous layer was
10 separated. The organic layer was washed with 3% NH₄OH (2 x 2.0 mL), water (2 x 10 mL), brine (2 x 10 mL), dried over MgSO₄, filtered and the solvent was evaporated. The resulting residue was dissolved in CH₂Cl₂ and flash chromatographed (7% MeOH/CH₂Cl₂, 0.5% NH₄OH) to give the crude product as a yellow oil. The material was again flash chromatographed (8% MeOH/CH₂Cl₂, 0.5% NH₄OH) to give the title
15 compound as a colorless foam (0.02 g, 41%).

20

METHODS OF USE

In accordance with the invention, there are provided novel methods of using the compounds of the formula (I). The compounds disclosed therein effectively block inflammatory cytokine production from cells. The inhibition of cytokine production is
25 an attractive means for preventing and treating a variety of cytokine mediated diseases or conditions associated with excess cytokine production, *e.g.*, diseases and pathological conditions involving inflammation. Thus, the compounds are useful for the treatment of diseases and conditions as described in the Background section, including the following conditions and diseases:
30 osteoarthritis, atherosclerosis, contact dermatitis, bone resorption diseases, reperfusion injury, asthma, multiple sclerosis, Guillain-Barre syndrome, Crohn's disease, ulcerative colitis, psoriasis, graft versus host disease, systemic lupus erythematosus and insulin-dependent diabetes mellitus, rheumatoid arthritis, toxic shock syndrome, Alzheimer's disease, diabetes, inflammatory bowel diseases, acute and chronic pain as well as
35 symptoms of inflammation and cardiovascular disease, stroke, myocardial infarction,

alone or following thrombolytic therapy, thermal injury, adult respiratory distress syndrome (ARDS), multiple organ injury secondary to trauma, acute glomerulonephritis, dermatoses with acute inflammatory components, acute purulent meningitis or other central nervous system disorders, syndromes associated with hemodialysis, leukopheresis, granulocyte transfusion associated syndromes, and necrotizing enterocolitis, complications including restenosis following percutaneous transluminal coronary angioplasty, traumatic arthritis, sepsis, chronic obstructive pulmonary disease and congestive heart failure. The compounds of the invention may also be useful for anticoagulant or fibrinolytic therapy (and the diseases or conditions related to such therapy) as described in US application no. 10/630,599 and PCT/US03/23841.

The compounds of the invention are also p38 MAP kinase inhibitors. Methods for screening p38 MAP kinase inhibitors are known in the art. As disclosed in the Background of the Invention, the compounds of the invention will therefore be useful for treating oncological diseases. These diseases include but are not limited to solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma and mesothelioma.

Examples of brain cancers include, but are not limited to brain stem, optic and hypophtalamic glioma, cerebella and cerebral astrocytoma, medulloblastoma, ependymoma, as well as pituitary, neuroectodermal and pineal tumor.

Examples of peripheral nervous system tumors include, but are not limited to neuroblastoma, ganglioneuroblastoma, and peripheral nerve sheath tumors.

Examples of tumors of the endocrine and exocrine system include, but are not limited to thyroid carcinoma, adrenocortical carcinoma, pheochromocytoma, and carcinoid tumors.

5 Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer.

Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

10 Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, and urethral cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

15 Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), hepatoblastoma, cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

20 Head-and-neck cancers include, but are not limited to laryngeal/hypopharyngeal/nasopharyngeal/oropharyngeal cancer, and lip and oral cavity cancer.

Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, Hodgkins lymphoma, cutaneous T-cell lymphoma, and lymphoma of the central nervous system.

25 Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, Ewings sarcoma, malignant fibrous histiocyoma, lymphosarcoma, angiosarcoma, and rhabdomyosarcoma. Leukemias include, but are not limited to acute myeloid leukemia,

acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

Plasma cell dyscrasias include, but are not limited to multiple myeloma, and Waldenstrom's macroglobulinemia.

- 5 These disorders have been well characterized in man, but also exist with a similar etiology in other mammals, and can be treated by pharmaceutical compositions of the present invention.

10 For therapeutic use, the compounds may be administered in any conventional dosage form in any conventional manner. Routes of administration include, but are not limited to, intravenously, intramuscularly, subcutaneously, intrasynovially, by infusion, sublingually, transdermally, orally, topically or by inhalation. The preferred modes of administration are oral and intravenous.

- 15 The compounds may be administered alone or in combination with adjuvants that enhance stability of the inhibitors, facilitate administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increase inhibitory activity, provide adjunct therapy, and the like, including other active ingredients. Advantageously, such combination therapies utilize lower
20 dosages of the conventional therapeutics, thus avoiding possible toxicity and adverse side effects incurred when those agents are used as monotherapies. The above described compounds may be physically combined with the conventional therapeutics or other adjuvants into a single pharmaceutical composition. Reference in this regard may be made to Cappola et al.: US patent application no. 09/902,822, PCT/US
25 01/21860 and US application no. 10/214,782, each incorporated by reference herein in their entirety. Advantageously, the compounds may then be administered together in a single dosage form. In some embodiments, the pharmaceutical compositions comprising such combinations of compounds contain at least about 5%, but more preferably at least about 20%, of a compound of formula (I) (w/w) or a combination
30 thereof. The optimum percentage (w/w) of a compound of the invention may vary and is within the purview of those skilled in the art. Alternatively, the compounds may be

administered separately (either serially or in parallel). Separate dosing allows for greater flexibility in the dosing regime.

As mentioned above, dosage forms of the compounds described herein include
5 pharmaceutically acceptable carriers and adjuvants known to those of ordinary skill in the art. These carriers and adjuvants include, for example, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, buffer substances, water, salts or electrolytes and cellulose-based substances. Preferred dosage forms include, tablet, capsule, caplet, liquid, solution, suspension, emulsion, lozenges, syrup, reconstitutable
10 powder, granule, suppository and transdermal patch. Methods for preparing such dosage forms are known (see, for example, H.C. Ansel and N.G. Popovich, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5th ed., Lea and Febiger (1990)). Dosage levels and requirements are well-recognized in the art and may be selected by those of ordinary skill in the art from available methods and techniques
15 suitable for a particular patient. In some embodiments, dosage levels range from about 1-1000 mg/dose for a 70 kg patient. Although one dose per day may be sufficient, up to 5 doses per day may be given. For oral doses, up to 2000 mg/day may be required. Reference in this regard may also be made to US application serial no.10/313,667. As the skilled artisan will appreciate, lower or higher doses may be required depending on
20 particular factors. For instance, specific dosage and treatment regimens will depend on factors such as the patient's general health profile, the severity and course of the patient's disorder or disposition thereto, and the judgment of the treating physician.

BIOLOGICAL ASSAYS

25

Inhibition of TNF Production in THP Cells

The inhibition of cytokine production can be observed by measuring inhibition of TNF α in lipopolysaccharide stimulated THP cells (for example, see W. Prichett *et al.*, 1995, *J. Inflammation*, 45, 97). All cells and reagents were diluted in RPMI 1640 with phenol
30 red and L-glutamine, supplemented with additional L-glutamine (total: 4 mM), penicillin and streptomycin (50 units/ml each) and fetal bovine serum (FBS, 3%) (GIBCO, all conc. final). Assay was performed under sterile conditions; only test

compound preparation was nonsterile. Initial stock solutions were made in DMSO followed by dilution into RPMI 1640 2-fold higher than the desired final assay concentration. Confluent THP.1 cells (2×10^6 cells/ml, final conc.; American Type Culture Company, Rockville, MD) were added to 96 well polypropylene round
5 bottomed culture plates (Costar 3790; sterile) containing 125 μ l test compound (2 fold concentrated) or DMSO vehicle (controls, blanks). DMSO concentration did not exceed 0.2% final. Cell mixture was allowed to preincubate for 30 min, 37°C, 5% CO₂ prior to stimulation with lipopolysaccharide (LPS; 1 μ g/ml final; Siga L-2630, from E.coli serotype 0111.B4; stored as 1 mg/ml stock in endotoxin screened distilled H₂O at
10 -80°C). Blanks (unstimulated) received H₂O vehicle; final incubation volume was 250 μ l. Overnight incubation (18 - 24 hr) proceeded as described above. Assay was terminated by centrifuging plates 5 min, room temperature, 1600 rpm (400 x g); supernatants were transferred to clean 96 well plates and stored -80°C until analyzed for human TNF α by a commercially available ELISA kit (Biosource #KHC3015,
15 Camarillo, CA). Data was analyzed by non-linear regression (Hill equation) to generate a dose response curve using SAS Software System (SAS institute, Inc., Cary, NC). The calculated IC₅₀ value is the concentration of the test compound that caused a 50% decrease in the maximal TNF α production.

20 Preferred compounds have an IC₅₀ < 1 μ M in this assay.

Inhibition of other cytokines

By similar methods using peripheral blood monocytic cells, appropriate stimuli, and
25 commercially available ELISA kits (or other method of detection such as radioimmunoassay), for a particular cytokine, inhibition of IL-1 β , GM-CSF, IL-6 and IL-8 can be demonstrated for preferred compounds (for example, see J.C. Lee *et al.*, 1988, *Int. J. Immunopharmacol.*, 10, 835).

30 All publications, patent publications and patent applications cited in this application are incorporated herein by reference in their entirety.